SPINOCEREBELLAR ATAXIAS

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SPINOCEREBELLAR ATAXIAS

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DECLARATION

This project was undertaken under the guidance of Prof Peter Beighton of the Department of Human Genetics, Medical School, University of Cape Town. The clinical survey was commenced on receipt of the K M Browse Research Scholarship from the South African College of Medicine from January 1987 to December 1988 and thereafter during my tenure as Senior Specialist in the Neurology Unit, Department of Medicine, Groote Schuur Hospital and University of Cape Town.

The HLA linkage study was conducted in collaboration with Dr R Martell, Principal Specialist, Cape Provincial Laboratory of Tissue Immunology. The laboratory investigations pertaining to the HLA typing, serum proteins, red blood cell antigens and red cell enzymes were done in the Cape Provincial Laboratory of Tissue Immunology.

The molecular study involving the microsatellite markers and the expanded trinucleotide repeats was undertaken in the molecular laboratory of the Department of Human Genetics of the University of Cape Town Medical School, under the supervision of Dr R. Ramesar. The author participated in the bench activities.

I certify that this is my own work and that it has not been presented for a degree at any other university.

Alan Bryer

May 1994

DEDICATION

To the memory of my late father-in-law,

Joseph Jonah Glick (1916-1988).

INDEX

	PAGE
ABSTRACT	IX
ACKNOWLEDGEMENTS	XI
ABBREVIATIONS AND SYMBOLS	XV
FIGURES AND ILLUSTRATIONS	XVII
TABLES	XIX
LAYOUT OF THESIS	XXII

SECTION I: INTRODUCTION

CHAPTER 1 REVIEW OF SPINOCEREBELLAR ATAXIA	2
1.1 Clinical definition and symptomatology	3
1.2 Phenotypic variety	3
1.3 Course and prognosis	4
1.4 Mode of inheritance	5
1.5 Pathogenesis	6
1.6 Neuropathology	7
1.7 Psychological implications	10
CHAPTER 2 THE AIMS OF THE STUDY	12
CHAPTER 3: HISTORICAL BACKGROUND AND NOSOLOGY	14
3.1 History	15
3.2 Nosology	16
3.3 Classification	18
CHAPTER 4 DEMOGRAPHY	26
4.1 Epidemiology of spinocerebellar ataxia	27
4.2 Prevalence of hereditary ataxia in Africa	28
4.3 Demography of the population of South Africa	29
4.4 Demography of the population of the Western Cape	34

SECTION II: PILOT STUDY

CHAPTER 5 RETROSPECTIVE PILOT STUDY	36
5.1 Background to pilot study	37
5.2 Objectives of the pilot study	37
5.3 Methods	38
5.4 Results of the pilot study	39
5.4.1 Familial cerebellar ataxia	40
5.4.2 Sporadic cerebellar ataxia	45

page

SECTION III: PROSPECTIVE SURVEY

CHAPTER 6 METHODOLOGY OF PROSPECTIVE ANALYSIS 51

6.1 Ascertainment of affected families 52
6.2 Diagnostic criteria 53
6.3 Clinical evaluation 54
6.3.1 General and neurological examination 54
6.3.2 Ataxia Severity Score 55
6.3.3 Optokinetic nystagmus and smooth pursuit eye movements 59
6.3.4 Assessment of visual function 62
6.3.5 Assessment of unaffected persons 62

CHAPTER 7 PROSPECTIVE ASSESSMENT OF AFFECTED FAMILIES 65

7.1 Symptomatology 67
7.1.1 Gait disturbance 68
7.1.2 Upper limb incoordination 70
7.1.3 Speech disturbance 70
7.1.4 Muscle cramps 70
7.1.5 Weakness 71
7.1.6 Urinary symptoms 71
7.1.7 Vision 71
7.1.8 Cognitive decline 72
7.2 Clinical signs 72
7.2.1 Gait 74
7.2.2 Limb ataxia 74
7.2.3 Dysarthria 78
7.2.4 Pyramidal tract signs and muscle weakness 78
7.2.5 Abnormal involuntary movements 79
7.2.6 Dysphagia and upper airway dysfunction 80
7.2.7 Sensory impairment 82
7.2.8 Ocular signs 83
7.2.9 Dementia 85
7.2.10 Evolution of the phenotype 87
7.3 Time to reach dependency 90
7.4 Deaths 90
7.5 Minimal prevalence 90
7.6 Conclusions 92

CHAPTER 8 PROSPECTIVE ASSESSMENT OF EIGHT AFFECTED FAMILIES WITH CLINICALLY DISTINCT PHENOTYPES 94

8.1 Late onset cerebellar ataxia without dysarthria and ocular signs 96
8.1.1 Phenotype of family K 96
8.1.2 Discussion of family K 98
8.2 Very late onset cerebellar ataxia with depressed reflexes 99
8.2.1 Phenotype of family L 99
8.2.2 Discussion of family L 100
8.3 Autosomal dominant ataxia with macular degeneration 100
8.3.1 Phenotype of family M 100

page

8.3.2 Discussion of family M 102
8.4 Autosomal dominant ataxia with macular degeneration and slow eye movements 104
8.4.1 Phenotype of family N 104
8.4.2 Discussion of family N 107
8.5 Cerebellar ataxia and hypogonadism 109
8.5.1 Phenotype of family O 109
8.5.2 Discussion of family O 111
8.6 Cerebellar ataxia, optic atrophy and deafness 114
8.6.1 Phenotype of family P 114
8.6.2 Discussion of family P 117
8.7 Cerebellar ataxia, mental retardation, motor neurone syndrome and macular degeneration 120
8.7.1 Phenotype of family Q 120
8.7.2 Discussion of family Q 122
8.8 Spastic paraparesis with ataxia and dystonia 125
8.8.1 Phenotype of family R 125
8.8.2 Discussion of family R 126
8.9 Conclusions 127

SECTION IV: SPECIAL INVESTIGATIONS

CHAPTER 9 DIAGNOSTIC IMAGING 129

9.1130 Introduction 130
9.1.1 Background to diagnostic imaging 130
9.2 Methods 132
9.2.1 Sample 132
9.2.2 Procedure and settings 133
9.2.3 Evaluation and scoring of scans 133
9.3 Results 134
9.3.1 Autosomal dominant ataxia 135
9.3.2 MRI scan of 4 individuals with distinct phenotypes 145
9.4 Discussion 146

CHAPTER 10 ELECTROPHYSIOLOGICAL STUDY 149

10.1 Introduction 150
10.2 Methods 151
10.2.1 Sample 151
10.2.2 Technique 152
10.3 Results 154
10.3.1 Nerve conduction studies in persons with the same phenotype 154
10.3.2 Nerve conduction studies in persons with distinct phenotypes 155
10.4 Discussion 156

SECTION V: LINKAGE STUDY

CHAPTER 11 LINKAGE ANALYSIS IN AFFECTED FAMILIES 159

11.1 Introduction 160
11.2 Methods 161
11.2.1 Linkage analysis with HLA, red blood cell and serum protein markers 161

page

11.2.2 Microsatellite DNA markers 163
11.2.3 Trinucleotide (CAG) expansion at SCA1 166
11.3 Results 167
11.3.1 Linkage analysis with HLA, red cell and serum protein markers 167
11.3.2 Linkage analysis with microsatellite markers 174
11.3.3 Trinucleotide expansion at SCA1 176
11.4 Discussion 182
11.4.1 HLA analysis 182
11.4.2 Linkage analysis with microsatellite markers 183
11.4.3 Trinucleotide expansion at SCA1 187
11.5 Conclusion 188

SECTION VI: PSYCHOLOGICAL SURVEY

CHAPTER 12 PSYCHOLOGICAL AND SOCIAL PERSPECTIVES 190

12.1 Introduction 192
12.2 Methods 194
12.2.1 Questionnaire design 194
12.2.2 Procedure 198
12.2.3 Sample 199
12.3 Results 202
12.3.1 Psychological impact on unaffected persons 202
12.3.2 Risk awareness of unaffected individuals 205
12.3.3 Preselection 207
12.3.4 Attitudes towards affected family members 208
12.3.5 Attitudes towards unaffected family members 209
12.3.6 Somatic complaints in unaffected individuals 209
12.3.7 Attitudes of unaffected persons to reproduction 210
12.3.8 Interviews with spouses 211
12.4 Discussion 212

SECTION VII: CONCLUSIONS

CHAPTER 13 CONCLUSIONS, APPLICATIONS AND RECOMMENDATIONS 217

13.1 Pilot study 218
13.2 Prospective survey 218
13.3 Diagnostic imaging and electrophysiological tests 219
13.4 Molecular linkage studies 220
13.5 Psychological survey 221
13.6 Practical applications and future objectives 222
13.6.1 Establishment of Neurogenetics clinic 222
13.6.2 Future studies 223
13.6.3 Establishment of a lay support group 224
13.6.4 Predictive testing 224

page

REFERENCES 230

APPENDIX

A1.1 Pedigrees (families A to X) ii

A1.2 Clinical Examination Protocol xiii

A1.3 Publications and Abstracts relating to this thesis xv

ABSTRACT

The adult onset familial spinocerebellar ataxias are an uncommon group of genetic disorders which have been well characterised in North America and Europe. Information concerning these conditions in Africa and other parts is scant. In order to address this problem, a large scale survey has been undertaken in the Western Cape region of South Africa. In this investigation more than 300 persons in 18 affected families have been appraised and investigated and the phenotypic features have been analysed in detail. In 10 of these families, the phenotype was similar and the remaining 8 had clinically distinct phenotypes. The morphological changes of the nervous system, present at different stages of the disorder, were shown on the MRI scans. Electrophysiologic studies demonstrated that a motor polyneuropathy was a variable, and usually late manifestation in persons with adult onset ataxia.

A minimum prevalence for the late onset hereditary ataxias was 24.68 per million for the population of the Western Cape at the end of December 1993.

Six South African families with the same phenotype were studied for linkage between SCA and the HLA locus. This analysis revealed linkage in one family only (lod score = 4.13 at $\theta = 0.05$).

Five of the largest South African families were then investigated for linkage to the highly informative PCR based dinucleotide repeat markers at the D6S89 and D6S260 loci on the short arm of chromosome 6. Allele frequencies for the 2 markers were established in the mixed ancestry population group and linkage was demonstrated in the 2 largest families. In family A, the maximum lod score for the D6S89 marker = 7.43 at $\theta = 0.0$ and the maximum lod score for the D6S260 marker = 6.11 at $\theta = 0.0$. In family B, the maximum lod score for the D6S89 marker = 3.8 at $\theta = 0.0$ and the maximum lod score for the D6S260 marker = 4.1 at $\theta = 0.0$. In the 3 smaller families the maximum lod scores at $\theta = 0.0$ were suggestive of linkage to the disorder. Results with the 2 microsatellite markers (D6S89 and D6S260) indicate that 2 different disease-associated haplotypes occur in the 5 families of mixed ancestry suggesting independent origins of the disorder.

Eleven South African families (8 families with the same phenotype and 3 with distinct phenotypes) were screened by PCR analysis for the presence of the expanded CAG repeat at the SCA1 locus. Definite cosegregation of the disorder with the CAG trinucleotide expansion at SCA1 occurred in 5 families all of whom had the same phenotype. The size of the repeats correlate inversely to the age of onset. In 6 of the 11 families, the disorder was not associated with the CAG expansion at SCA1. The disorder in 3 of the 6 kindred was clinically indistinguishable from that in the families found to have the trinucleotide expansion. The relatively simple resolution of the CAG repeats associated with the disorder provides an accurate tool for predictive testing.

The data obtained from the questionnaire survey indicates the profound psychological impact of the disorder on unaffected family members. The majority of the family members surveyed had a very poor understanding of the genetic nature of the disorder and 80% of the unaffected persons had incorrect perceptions of personal risk status. The survey revealed that the disorder had little impact on the attitudes of both affected and unaffected persons concerning reproduction. Many factors influence the responses of those persons at risk. The psychological survey has identified several issues which will be addressed prior to the introduction of a predictive testing service for the familial ataxias in South Africa.

The results of this study have provided data on the clinical spectrum and natural history of the late onset familial ataxias in the Western Cape region of South Africa. This has facilitated improved genetic counselling of both affected and unaffected persons at the recently established Groote Schuur Hospital Neurogenetics Clinic.

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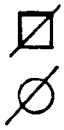
ABBREVIATIONS AND SYMBOLS

ADCA	autosomal dominant cerebellar ataxia
alpha-dCT^{32}P	deoxycytidine 5'[alpha-^{32}P] triphosphate
bp	base pairs
°C	degree Celsius
CAG	Cytosine Adenine Guanine
CMAP	compound motor action potential
cM	centiMorgan
cm	centimetre
CT	computerized tomography
DNA	deoxyribonucleic acid
dNTPs	deoxyribonucleoside-5'-triphosphates
EMG	electromyography
GSH	Groote Schuur Hospital
HLA	human leukocyte antigens
HCl	hydrochloric acid
hr	hour/s
KCl	potassium chloride
Lod score	The $\log_{10}$ of the likelihood ratio
MEPS	maximum expiratory pressures
MELAS	mitochondrial encephalopathy with lactic acidosis and stroke like episodes
MERRF	myoclonic epilepsy and ragged red fibers
$MgCl_2$	magnesium chloride
MIPS	maximum inspiratory pressures
MRI	magnetic resonance imaging
µC	microCurie
µl	microlitre
µM	micromolar

mM	millimolar
mm	millimetre
ms	millisecond
min	minute/s
NCV	nerve conduction velocity
nmol/l	nanomoles per litre
no.	number
OPCA	olivopontocerebellar atrophy
OKN	optokinetic nystagmus
PCCA	parenchymatous cerebellar cortical atrophy
PCR	polymerase chain reaction
SA	South Africa
SCA	spinocerebellar ataxia
SCA1	autosomal dominant gene locus on chromosome 6p
TR	tendon reflexes
UCT	University of Cape Town
WFN	World Federation of Neurology
WHO	World Health Organisation

	unaffected male
	unaffected female
	affected male
	affected female
	sex unspecified
	male - deceased
	female - deceased
θ	recombination fraction

FIGURES AND ILLUSTRATIONS

		page
Figure 4.1	Map of the Republic of South Africa	32
Figure 4.2	Map of the Western Cape Region	33
Figure 6.1	Clinical assessment of an unaffected family member.	63
Figure 6.2	The "team" en route to a peripheral clinic	63
Figure 7.1	An affected person with a broad based gait	75
Figure 7.2	Copied diagrams - examples from different individuals with mild to severe ataxia	76
Figure 7.3	Circle and dot test	78
Figure 7.4	Flow-Volume Loop of an affected person with recurrent aspiration pneumonia	81
Figure 7.5	Three affected persons with "Staring" eyes	84
Figure 7.6	Evolution of the phenotype	89
Figure 8.1	Proband and cousin (Family N)	106
Figure 8.2	"Bulls-eye" maculopathy	106
Figure 8.3	Impaired lateral gaze	107
Figure 9.1	MRI scan : Normal scan	139
Figure 9.2	MRI scan : mild atrophy of the cerebellum and brainstem	140
Figure 9.3	MRI scan : moderate atrophy of cerebellum and brainstem	141
Figure 9.4	MRI scan : severe atrophy of cerebellum and brainstem	142
Figure 9.5	MR scan : mild, moderate, and severe atrophy of the spinal cord	143
Figure 10.1	Nerve conduction studies: Groote Schuur Hospital, EMG laboratory	153
Figure 11.1	Postulated HLA haplotypes in Family A	170

		page
Figure 11.2	Autoradiograph indicating expanded trinuleotide repeats	178
Figure 11.3	Correlation between the age of onset and the number of CAG repeats	180
Figure 11.4	Correlation between the duration of the disorder and the number of CAG repeats	181
Figure 12.1	Four of the participants in the survey	201

TABLES

		page
Table 1.1	Types of Hereditary Ataxia	5
Table 3.1	Variables used in ataxia classifications	19
Table 3.2	Classification of hereditary ataxia (Harding)	20
Table 3.3	WHO proposed classification	23
Table 3.4	WFN classification of hereditary ataxias and familial spastic paraplegias	23
Table 4.1	Population of Republic of South Africa	31
Table 4.2	Population of the Western Cape by ethnic group	34
Table 5.1	Ethnic group and sex of persons with familial ataxia (pilot study)	40
Table 5.2	Symptoms of familial cerebellar ataxia (pilot study)	41
Table 5.3	Clinical signs of familial cerebellar ataxia (pilot study)	42
Table 5.4	Ethnic group and sex of persons with sporadic ataxia	45
Table 5.5	Clinical manifestations of sporadic ataxia	46
Table 6.1	Ataxia severity score	58
Table 7.1	Symptoms of familial late onset cerebellar ataxia in families with the same phenotype	68
Table 7.2	Clinical signs of familial late onset spinocerebellar ataxia	73
Table 7.3	Ocular signs in familial late onset spinocerebellar ataxia	73
Table 7.4	Severity of ataxia at prospective assessment	73
Table 7.5	Lung functions on an individual with recurrent aspiration pneumonia	81
Table 9.1	MRI settings	133

		page
Table 9.2	Correlation table for the scoring of cerebellar atrophy	135
Table 9.3	Correlation table for the scoring of brainstem atrophy	136
Table 9.4	Correlation table for the scoring of spinal cord atrophy	136
Table 9.5	Correlation table for the scoring of cerebral cortex atrophy	136
Table 9.6	Correlation table of global scores and averaged global scores	137
Table 9.7	MRI morphology of late onset dominant ataxia	138
Table 9.8	Comparison of clinical and radiographic indices	145
Table 10.1	Severity of ataxia in sample	151
Table 10.2	Nerve conduction studies: normal values (GSH laboratory)	153
Table 10.3	Nerve conduction study results	154
Table 11.1	PCR conditions for microsatellite markers	165
Table 11.2	HLA haplotypes of those family members who were tested	168
Table 11.3	Lod scores obtained with markers situated on the short arm of chromosome 6	169
Table 11.4	Results of linkage analysis in family A with non-HLA markers	172
Table 11.5	Lod scores for HLA markers	173
Table 11.6	Marker alleles: number and size range of alleles in the South African background mixed ancestry population and in the ataxia families	174
Table 11.7	Allele frequencies in the South African mixed ancestry population	174
Table 11.8	Alleles segregating with the SCA phenotype	175

		page
Table 11.9	Results of linkage analysis between SCA and microsatellite markers D6S89 and D6S260	175
Table 12.1	Age and sex of sample	199
Table 12.2	Occupational level of the persons in the sample	200
Table 12.3	Assigned risk status of unaffected persons	200
Table 12.4	Psychosocial impact of the disorder on the lives of unaffected persons	202
Table 12.5	Problems facing affected persons	203
Table 12.6	Major problems for families of affected individuals	204
Table 12.7	Perceived risk status of unaffected individuals	206
Table 12.8	"True" vs "Perceived" risk status	207
Table 12.9	Somatic complaints in unaffected persons	210
Table 12.10	Attitudes of unaffected individuals towards reproduction	210

LAYOUT OF THESIS

The layout of this thesis has been planned to facilitate ease of reading and to avoid unnecessary duplication of data. For this reason, the Tables and Figures pertinent to each chapter are interspersed with the text and there is extensive cross-referencing between chapters.

The thesis is divided into seven sections. Section I is a review of the subject and the aims of the present study. A retrospective pilot study of individuals with familial ataxia who were assessed at Groote Schuur Hospital over a 10 year period is presented in Section II. The prospective clinical survey of the late onset familial ataxias is presented in Section III, followed by the special investigations (diagnostic imaging and neurophysiological tests) of affected persons in Section IV. Section V is a molecular linkage study in 5 families with hereditary ataxia. The psychological survey of a group of unaffected and affected persons with ataxia is in Section VI. Section VII is concerned with the conclusions, practical applications and recommendations of the study.

BIBLIOGRAPHY:

In the bibliography the references are listed alphabetically by first author. Standard abbreviations are used for journal names in accordance with current convention. Where the number of authors exceed 5, the names of the first 4 authors are cited, followed by et al. In the text, if multiple authors

are responsible for an article, then the first author is cited followed by "et al".

Appendix:

The pedigrees of all the families described in this project are illustrated in the appendix. Protocols of investigation, and a list of previously published manuscripts and papers presented at scientific meetings relating to this study appear in the appendix.

This investigation was undertaken with the approval of the Research and Ethics Committee of the University of Cape Town, Medical School.

SECTION I

INTRODUCTION

Chapter 1 REVIEW OF SPINOCEREBELLAR ATAXIA

Chapter 2 THE AIMS OF THE STUDY

Chapter 3 HISTORICAL BACKGROUND AND NOSOLOGY

Chapter 4 DEMOGRAPHIC ASPECTS OF SPINOCEREBELLAR ATAXIA IN SOUTH AFRICA

CHAPTER 1 REVIEW OF SPINOCEREBELLAR ATAXIA

		Page
1.1	Clinical definition and symptomatology..	3
1.2	Phenotypic variety.....	3
1.3	Course and prognosis.....	4
1.4	Mode of inheritance.....	5
1.5	Pathogenesis.....	6
1.6	Neuropathology.....	7
1.7	Psychological implications.....	10

CHAPTER ONE

REVIEW OF SPINOCEREBELLAR ATAXIA

1.1 CLINICAL DEFINITION AND SYMPTOMATOLOGY

The hereditary late onset spinocerebellar ataxias are a heterogeneous group of progressive neurologic disorders in which cerebellar ataxia is the predominant manifestation.

Affected individuals suffer from progressive gait and limb ataxia and dysarthria. Many different phenotypes have been identified. The cerebellar signs may be accompanied by a wide variety of other symptoms and signs, depending on the particular phenotype, the extent of the pathology and the duration of the disorder. These include pyramidal and extrapyramidal signs, ophthalmoplegia, optic atrophy, dementia, peripheral neuropathy, amyotrophy, lateral and dorsal column involvement and deafness (Schut, 1954; Currier et al., 1972; Nino et al., 1980; Berciano, 1982a; Zoghbi et al., 1988).

1.2 PHENOTYPIC VARIETY

The age of onset, clinical features and rate of progression may vary from family to family. Even within a given family there may be considerable variation in phenotypic expressivity with regard to the onset of the disorder, extent of the

clinical and pathological manifestations as well as the course and prognosis (Diaz et al., 1990). Infrequently there is a characteristic clinical syndrome in the majority of the affected family members and a different phenotype in one or several other members (Rosenberg, 1990). Currier et al.(1972) described clinical features in members of a kindred who became affected at a younger age which differed from those persons who were older when they developed signs of the disease.

1.3 COURSE AND PROGNOSIS

In the late onset autosomal dominant variety of spino-cerbellar ataxia the onset of the disorder is usually in the 3rd or 4th decade but may be as early as 15 years of age (Haines et al., 1984; Nino et al., 1980; Currier et al.,1972). Most patients present with progressive ataxia of gait and this is invariably associated with dysarthria. The majority of persons are unable to walk unaided within 15 years of onset. In the well-studied Schut-Swier kindred patients were confined to a wheelchair within 10 to 15 years of onset. Speech becomes unintelligible and the upper limbs useless because of marked incoordination. Ultimately aspiration of food leads to frequent bouts of pneumonia and choking is likely. Life expectancy is shortened; Harding (1984a) has recorded a mean age of death at 57.43 years +/- 13.19 years. In other families a younger average age of death (viz. 39years) was documented (Haines et al.,1984). In certain kindreds the evidence suggests that the rate of progression of the disease is more rapid the younger the age of onset (Zoghbi et al.,

1988; Diaz et al., 1990). Death usually results from pneumonia (Haines et al., 1984).

1.4 MODE OF INHERITANCE

Recognizable modes of inheritance in the hereditary spinocerebellar ataxias are autosomal dominant, autosomal recessive and rarely, X-linked recessive (Lutz et al., 1989; Apak et al., 1989). The nosology of the spinocerebellar ataxias is complex and this issue is addressed at length in chapter 3. For the sake of clarity a simplified list of the different forms of this condition are given in table 1.1.

TABLE 1.1 TYPES OF HEREDITARY ATAXIA

1. Hereditary congenital nonprogressive ataxias
2. Friedreich's Ataxia
3. Childhood onset recessive ataxias (non-Friedreich's)
4. Adult onset recessive or sporadic ataxias
5. Adult onset dominant ataxia - common type
6. Adult onset dominant ataxias - other types

Friedreichs ataxia, an early onset cerebellar ataxia, is an autosomal recessive disease. The majority of the familial late onset (usually after the age of 20 years) cerebellar ataxias show an autosomal dominant inheritance pattern. Sporadic examples of late onset cerebellar ataxia are common. This situation poses considerable difficulty for the genetic counselling of these individuals and their families.

In those families with an autosomal dominant inheritance, clinical examination of the asymptomatic members at risk is generally unhelpful in predicting whether or not they will develop the disorder in the future.

1.5 PATHOGENESIS

The aetiology of this group of conditions remains undetermined and at present the putative genes and their products have not been identified. In the autosomal dominant group of late onset cerebellar ataxias there has been much speculation whether the phenotypic variability can be explained by a single gene mutation in which many host factors modify the expression and penetrance of the mutant gene or whether the phenotypic variation between different families can be attributed to different mutations.

The advent of recombinant DNA technology has made the investigation of the aetiology of the genetically determined neurodegenerative disorders a realistic proposition. This rapidly advancing technology has lead to the cloning of the disease genes in a number of these conditions, notably, Huntington disease. Similar genetic localization studies are presently being undertaken for the familial ataxias. Various biochemical and other parameters implicated in the pathogenesis have also been studied in different kindreds. Examples of these studies include: the rate of cerebellar glucose metabolism utilizing labelled glucose and positron emission tomography (Gilman et al., 1988); the activity and

concentration of certain enzymes, amino acids, and neurotransmitter substances in post mortem brain samples (Kish et al., 1987, 1988, 1991; Perry, 1984); glutamate dehydrogenase activity in peripheral leukocytes and fibroblasts as well as brain homogenates (Plaitakis et al., 1980, 1984; Duvoisin et al., 1983; Maruyama and Yamaguchi, 1984; Finocchiaro et al., 1986; Grossman et al.,1987; Rosenberg and Banner, 1989); abnormalities of urinary glycolipid content (Berenberg et al., 1984); and the density of different cerebellar receptors (Whitehouse et al., 1986; Makowiec et al., 1990). Although these findings are of value in understanding aspects of the pathogenesis, they have not aided the delineation of the molecular genetics (Rosenberg, 1990) in that these receptor or biochemical alterations may represent a genetic epiphenomenon. Even in diseases in which the specific biochemical defect is known (eg. abetalipo-proteinaemia), the relationship between the clinical and pathologic features and the biochemical defect is not fully understood (Berenberg et al., 1984). Biochemical abnormalities, however, provide clues to the pathogenesis of the disease process and may serve as markers for the underlying genetic defect.

1.6 NEUROPATHOLOGY

The neuropathology in this group of diseases is characterized by a loss of neurones in the cerebellar cortex, basis pontis and inferior olivary nuclei. Some neuronal loss may also occur in the spinal cord, cerebral cortex and basal ganglia.

The outstanding feature on microscopy is the loss of Purkinje cells in the cerebellum which may be so extensive that none can be found (Koeppen and Barron, 1984; Koeppen and Turok, 1992). Pathogenesis is a dynamic process that is inadequately explored by the gross and microscopic study of tissues. Individuals who die from hereditary ataxia generally reveal the morphologic end-stage of their illness, though early death by suicide or intercurrent illness has come to attention from time to time (Koeppen and Turok, 1992). Subramony et al.(1986) have reported a case of an 18 year old man who died from a self inflicted gunshot wound to the chest. While not ataxic prior to death, he was thought to be at high risk for dominant ataxia due to his HLA genotype. The cerebellar cortex revealed considerable Purkinje cell loss, suggesting that neuronal atrophy antedates the onset of ataxia and that a certain degree of neuronal depletion must be reached for first symptoms to be become manifest.

The morphology and pathology of the various subgroups of familial ataxia has been extensively discussed in the literature since the late 19th century.
Menzel described the pathology of a case of hereditary ataxia in 1891 and Dejerine and Thomas reported a similar sporadic case in 1900 and first used the term "atrophie olivo-ponto-cerebelleuse". In both familial and sporadic cases there was symmetrical atrophy of the cerebellum affecting the hemispheres more than the vermis with severe atrophy of the middle cerebellar peduncle, basis pontis and inferior olive and partial atrophy of the restiform body. A stream of similar

reports followed. These reports have differed in the extent of the atrophic process and the clinical manifestations. Olivopontocerebellar atrophy is a label which has remained firmly entrenched in the literature, although it is now recognized as not being a unitary morbid entity (Duvoisin, 1987). The olivopontocerebellar atrophies comprise a heterogeneous group of familial and sporadic disorders sharing major clinical and morphologic features (see chapter 3.2). A fundamental problem with the label "olivopontocerebellar atrophy" has been the enormous variation in the pathologic changes, even within the same kindred .

The earlier classifications were based on the pathological studies and the monumental works by Greenfield (1954) and Koningsmark and Weiner (1970) are two often quoted examples (see chapter 3.3). Harding reviewed the wide spectrum of pathological changes reported in the different kindreds with late onset autosomal dominant cerebellar ataxia (1984a). The neuropathology of the olivopontocerebellar atrophies has also been reviewed in detail by Koeppen and Barron (1984) and includes a discussion of the gross and microscopic pathology and electron microscopy findings. Despite the known heterogeneity of the morphological alterations in hereditary ataxia, certain trends can be recognized: The autosomal dominant forms, perhaps with the exception of "spastic ataxia", tend to have severe lesions of cerebellar cortex, while the dentate nucleus is usually unaffected. In contrast, the cerebellar cortex is variably involved in Friedreich's ataxia or is entirely normal but the dentate nucleus may be

quite seriously affected. Machado-Joseph disease is an autosomal dominant form of ataxia in which the dentate nucleus is more severely affected than the cerebellar cortex (Koeppen and Turok, 1992). In this disorder, there is also neuronal loss and gliosis in the substantia nigra, motor cranial nuclei, and neostriatum (Rosenberg, 1992).

As this topic has been extensively reviewed in the literature and as the scope of this thesis does not include a pathologic study, the author has omitted any additional review of the wide spectrum of neuropathology observed in this group of disorders.

1.8 PSYCHOSOCIAL IMPLICATIONS

There are enormous psychosocial implications for members of families with familial adult onset cerebellar ataxia. By the time the patients develop symptoms of the disease they have often procreated. Their children become aware of the threat of potential calamity as they are faced with observing their affected parent's gradual decline and know that they too may succumb to a similar fate. Clinicians who have worked with such families are well acquainted with the feelings of guilt, anxiety and depression that are generated in members of such a kindred. In unsophisticated communities family members frequently do not seek genetic counselling. Individuals at risk are often unaware or uninformed of their relative risk for developing the disorder. These issues are addressed in greater detail in chapter 12.

Clinical examination of asymptomatic individuals at risk does not reliably predict whether they will develop the disorder. Some studies have reported the presence of subtle clinical or physiologic "markers" (eg.:abnormal ocular motility, defective optokinetic nystagmus and absent or abnormal oculo-vestibular reflexes) to predict the development of the disorder in presymptomatic young adults in different kindred (Philcox et al., 1975; Hotson et al., 1987; Hutton et al., 1987). The presence of such abnormalities in asymptomatic individuals may well have ominous significance, but it is uncertain whether these findings constitute a consistent presymptomatic feature in this heterogeneous group. Furthermore, it is unclear for what duration of time these clinical "markers" are present prior to the individual becoming symptomatic.

Providing optimal genetic information to individuals at risk remains a primary goal to all those dealings with such patients and their kindred. As with other neurodegenerative disorders for which no cause or treatment is known the advent of a suitable genetic marker for prenatal and presymptomatic diagnosis would be invaluable.

CHAPTER 2

THE AIMS OF THE STUDY

The inherited cerebellar ataxias are an uncommon group of disorders which have been well characterized in North America and Europe (see chapter 4). Prior to this study, however, there has been no collective information concerning the clinical diversity, natural history, prognosis and genetic pattern of this disease in the population of South Africa (see 4.2). The author became interested in this group of conditions after observing that a significant number of patients with familial ataxia were attending the Groote Schuur Hospital neurology outpatient service. Although a tertiary referral centre will tend to accumulate unusual disorders, the author wondered whether there was not a pocket of families with ataxia within the local population of the Western Cape region, as the other neurologists at the clinic reported similar experience.

The aims of this investigation were as follows:

1. To survey the familial late onset cerebellar ataxias and clinically appraise and investigate all affected individuals and their kindred. In this way the different phenotypes within the population of the Western Cape could be documented.

2. To establish the mode of genetic transmission in the affected families.

3. To document the natural history and prognosis of the various subgroups.

4. To perform appropriate electrophysiological evaluation (EMG and nerve conduction velocities) in order to further delineate the phenotype.

5. To document the neuroradiologic findings in affected patients with particular reference to MRI imaging.

6. To determine the prevalence of the various forms of the condition in the Western Cape of South Africa.

7. To study the families by conventional and molecular linkage in the evaluation of heterogeneity in the disorder.

8. To identify reliable genetic markers which could be used for presymptomatic and prenatal diagnosis.

9. To establish a community record of all identified kindreds and to inform affected individuals and their families of the medical and genetic implications of the disorder.

CHAPTER 3: HISTORICAL BACKGROUND AND NOSOLOGY

"It is a commonplace that no differential diagnosis is possible during life between the different forms of cerebellar and spinocerebellar disease." (Greenfield, 1954).

"It is no exaggeration to state that there are as many classifications as there are authors on the subject. (Refsum and Skre, 1978)."

"These problems (of classification) have been magnified by the large numbers of descriptions of patients with a bewildering variety of hereditary ataxias." (Harding, 1982).

"This chapter ("classification of ataxia") is printed with apologies to Barbeau, Bell and Carmichael, Brouwer and Bemed, Eadie, Greenfield, Harding, Holmes, Koningsmark and Weiner, Netsky, Plaitakis, Schut, Sjogren, Sobue, Zulch and others who have previously attempted the clarification of chaos." (Currier, 1984).

		Page
3.1	History	15
3.2	Nosology	16
3.3	Classification	18

CHAPTER 3

HISTORICAL BACKGROUND AND NOSOLOGY

3.1 HISTORY

The early descriptions of the ataxias have their roots in the 19th century European schools of Neurology of France and Germany. Nicolaus Friedreich (1825-1882), Professor of Medicine at Heidelberg, was the first to describe an inherited ataxia in 1863. The autosomal recessive disorder which to this day bears his name was at first disputed by his European colleagues (Friedreich made a distinction between his cases and those with "locomotor ataxie"). The great French neurologist Charcot (1825-1893) finally conceded the existence of Friedreich's ataxia as a separate entity in 1884. In 1893 Charcot's pupil and subsequent successor to the Chair of Neurology at the Salpetriere, Pierre Marie (1853-1940) drew attention to a heterogeneous group of previously reported patients with manifestations clinically and pathologically distinct from Friedreich's ataxia. The onset of the symptoms was later in the 3rd decade and the disorder was usually inherited as an autosomal dominant trait. Although these cases represented a heterogeneous group the concept of Marie's ataxia is still used by some authors to this day.

Sir Gordon Holmes (1876-1966), a leader of modern English Neurology and physician at the National Hospital for Nervous Diseases for more than 40 years, wrote extensively on

cerebellar disease and the localization of function in the cerebellum. Holmes identified an autosomal recessive form of hereditary ataxia which was associated with hypogonadism, and he also proposed a classification for cerebellar disorders (Holmes, 1907). Many other attempts at classifications of the hereditary ataxias have followed and this topic remains a contentious and problematic issue to this day (see 3.3).

3.2 NOSOLOGY

In his monograph, Greenfield (1954) used the term spinocerebellar degeneration to include the group of familial and sporadic "progressive diseases characterized clinically by disturbances of the co-ordination of movement, or ataxia, and pathologically by degeneration of those afferent and efferent neuronal systems on which the smooth and efficient regulation depends". This label is still used by the National Library of Medicine, Washington as a subject heading in Index Medicus. The early descriptions of the inherited ataxias have been followed by a vast number of descriptions with many different phenotypes appearing in the literature. As Harding has pointedly noted, many of these cases appeared to be the same syndrome but have been given different labels by different authors. This has even happened to members of the same families.

The nosologic label, olivopontocerebellar atrophy appears frequently in reports. Debate about the ongoing use of this label has enlivened the literature. Duvoisin (1987) has argued

that the diversity of the morbid entities to which the term is applied calls for an attempt to define the syndrome in clinical terms. He suggested that the essential feature required is cerebellar involvement, either reflected clinically or demonstrated on CT or MRI scan, showing atrophy of the cerebellum and pons. High resolution CT and MRI are able to demonstrate the gross anatomic pathology which first defined this syndrome. In addition to the cerebellar signs, affected persons should show involvement of the extrapyramidal system which manifests usually as bradykinesia and rigidity and occasionally chorea or even dystonia. Additional systems involved include, the pyramidal, autonomic and peripheral nervous systems. Dementia, myoclonus, palatal myoclonus and amyotrophy may also occur but are less distinctive manifestations. Duvoisin (1987) concedes that the extra-pyramidal features may be lacking or masked by prominent cerebellar signs, and that the sequence with which different systems are affected in the course of the disease may vary giving rise to difficulties with the clinical diagnosis of this entity.

Harding (1987) has argued strongly against the application of pathological labels to living people since the pathology is no more specific than the clinical features in reflecting the basic disease defect and varies both within and between kindred. The term olivopontocerebellar atrophy is incomplete in describing the pathological features to which it has been applied as there may be associated degenerative changes in the basal ganglia, dentate nucleus, cerebral cortex, spinal cord

or peripheral nerves which are the rule rather than the exception (Koeppen and Barron, 1987). This situation is complicated by the lack of agreement in the interpretation of autopsy findings amongst several authors (Koeppen, 1984). Pathologically olivopontocerebellar atrophy can be found in a number of aetiologically distinct degenerative ataxic disorders (van Rossum et al., 1981; Harding, 1982) as well as in cases of progressive autonomic failure and striatonigral degeneration. Harding has suggested that inappropriate nosologic labels which stand the test of time and are easily understood by all who use them are acceptable and useful, provided they are mishandled consistently. She does not believe that this holds true for the term "olivopontocerebellar atrophy" as clinicians' views of what constitutes olivopontocerebellar atrophy are often defined by whatever clinical signs are observed in the particular group of patients they are likely to see with this type of disorder. Duvoisin's requirement for extrapyramidal involvement, for example, is not borne out by other reviews of the clinical features of the syndrome (Berciano, 1982).

3.3 CLASSIFICATION

The issue of the classification of the hereditary ataxias has been passionately debated for many years. Attempts at this task have resulted in more than 16 classifications. None are entirely satisfactory. A variety of parameters have been used to categorize different subgroups resulting in scholarly but diverse approaches (see table 3.1).

TABLE 3.1
SUMMARY OF VARIABLES USED IN ATAXIA CLASSIFICATIONS

Common vs. rare
Stationary vs. progressive
Hereditary vs. non-hereditary
Inheritance type
Gene locus
Age of onset
Clinical variations
Chemical subtypes
Pathology variations

Early classifications based primarily on pathology have been followed by attempts at a more broadly based classification incorporating clinical, genetic and biochemical data (Greenfield, 1954; Koningsmark and Weiner, 1970; Harding,1983; Barbeau, 1982; Currier 1984). The limitations of current classifications and their need for a working system has been debated and discussed at length in the literature.

Harding (1984) presents a strong argument against the continued use of a pathological classification for the late onset autosomal dominant cerebellar ataxias. As previously mentioned, pathological labels are invariably incomplete in describing the extent of the pathological features, and she questions the accuracy and wisdom of applying pathological labels to living patients. It is well known that there is considerable variability in the pathological findings even within a given family, and there has also been considerable disagreement with the interpretation of the neuropathology. Harding has utilized a combination of clinical and genetic parameters in her approach to classification which is presented in table 3.2. Autosomal recessive late onset cerebellar ataxias are thought to be exceptionally rare. The

clustering of clinical features was used to create the different subgroups for patients with a progressive unremitting cerebellar ataxia, autosomal dominant inheritance, and an onset after the age of 20.

Ataxic disorders in Harding's classification which are due to known metabolic defects have been omitted from table 3.2 as these disorders are not pertinent to this thesis. In particular, they usually present in the first or second decade and have characteristic clinical, radiological or biochemical features which identify them.

TABLE 3.2 CLASSIFICATION OF THE HEREDITARY ATAXIAS (Harding 1982)

ATAXIC DISORDERS OF UNKNOWN AETIOLOGY

A. Early onset cerebellar ataxia (onset usually before 20 years)

i.	Friedreich's ataxia
ii.	Early onset cerebellar ataxia with retained tendon reflexes
iii.	With hypogonadism +/- deafness and/or dementia
iv.	With myoclonus (Ramsay Hunt syndrome, Baltic myoclonus)
v.	With pigmentary retinal degeneration +/- mental retardation and/or deafness
vi.	With optic atrophy +/- mental retardation
vii.	With cataracts and mental retardation (Marinesco-Sjogren syndrome)
viii.	With childhood onset deafness and mental retardation
ix.	With congenital deafness
x	With extrapyramidal features
xi.	X-linked recessive spinocerebellar ataxia

B. Late onset cerebellar ataxia (onset usually after 20 years)

i. Autosomal dominant cerebellar ataxia with optic atrophy /ophthalmoplegia / dementia / extrapyramidal features / amyotrophy (probably includes Azorean ataxia) (ADCA type 1)

ii. Autosomal dominant cerebellar ataxia with pigmentary retinal degeneration +/- ophthalmoplegia and / or extrapyramidal features (ADCA type II)

iii. 'Pure' autosomal dominant cerebellar ataxia of later onset (over 50 years) (ADCA type III)

iv. Autosomal dominant cerebellar ataxia with myoclonus and deafness (ADCA type IV)

v. Autosomal dominant cerebellar ataxia with essential tremor

vi. Periodic autosomal dominant ataxia

This classification, which has departed from the traditional eponymous and pathological labels, has been criticized for the inequality in the numbers of kindred within each subgroup. The majority of kindred would be classified as having autosomal dominant cerebellar ataxia type 1 with only a few kindred falling into the remaining 5 categories. The inclusion of Machado-Joseph disease into subgroup autosomal dominant type I has also been controversial as this group has a high incidence of dystonia and amyotrophy (Nakano et al., 1972; Coutino and Andrade, 1978; Rosenberg 1976,1978,1991). Harding has pointed out that these features are not confined to patients from the Azores. Nevertheless, she has reiterated that her classification is provisional and awaits the identification of special genetic markers for these conditions, and that it may well be wise to regard each family as having its own specific mutation until there is evidence to the contrary.

Subramony and Currier (1991) have reviewed the different variables which have been used for the arrangement of categories and have proposed a classification incorporating proposals from the World Federation of Neurology (1985 meeting) and the World Health organization (1989 see table 3.3). They sought to adhere to the format of the new International Classification of Diseases (ICD-10) and have attempted to achieve a more balanced number of persons within each category. There is general agreement for the need of a classification which is clinically useful so that the physician can easily and correctly categorize affected persons with familial ataxia. Many of the previous classifications were large, complex and therefore somewhat imperfect in this regard. Currier's proposals were discussed at length at a meeting of the Heredoataxia Research Group of the WFN in Vancouver in September 1993. Following this discussion a new classification based on frequency, age of onset, gene loci and heredity was approved (see Table 3.4). It allows for expansion so that newly described syndromes can be added to the different rubrics and its use was recommended on a trial basis with the intent of eventual incorporation into the International Classification of Diseases.

TABLE 3.3

WHO PROPOSED CLASSIFICATION (1989)

G11 Hereditary ataxias and paraplegia
Excludes:hereditary and idiopathic neuropathy (G60.-)

G11.0 Congenital nonprogressive ataxia
Excludes: infantile cerebral palsy (G80.-)

G11.1 Early-onset cerebellar ataxia
Note:onset usually before 20 years

Early-onset cerebellar ataxia with retained tendon reflexes
Friedreich's ataxia (autosomal recessive)

With:
essential tremor
myoclonus (Hunt's ataxia)
X-linked recessive spinocerebellar ataxia

G11.2 Late-onset cerebellar ataxia

Note: onset usually after 20 years

G11.3 Cerebellar ataxia with defective DNA repair
Ataxia telangiectasia (Louis-Bar syndrome)

G11.4 Hereditary spastic paraplegia

G11.8 Other hereditary ataxias

G11.9 Hereditary ataxia, unspecified

TABLE 3.4

CLASSIFICATION OF HEREDITARY ATAXIAS AND FAMILIAL SPASTIC PARAPLEGIAS
WFN: HEREDOATAXIA RESEARCH GROUP 1993

G.11.0 Hereditary congenital nonprogressive ataxias
Chromosomal loci to be determined

G11.1 Recessive Friedreich's phenotype
.10 9th chromosome typical Friedreich's, onset before age 20
.11 9th chromosome Friedreich's,onset after age 20
.12 8th chromosome vitamin E deficiency, Friedreich's phenotype
.13 et seq. Other types and loci

G11.2 Childhood onset recessive ataxias, non-Friedreich's
.20 ataxia telangiectasia, 11th chromosome
.201 other gene locus ataxia telangiectasia
.21 autosomal recessive spastic ataxia of Charlevoix-

Saguenay (9th chromosome excluded)
.22 Other childhood onset recessive with retained reflexes
.23 et seq. Other types and loci

G11.3 Adult onset recessive or sporadic ataxias non-Friedreich's
.30 Adult onset recessive ataxia with retained reflexes
.31 Multiple system atrophy (sporadic)
.32 Sporadic adult onset ataxia - non multiple system atrophy
.33 et seq. Other types and loci

G11.4 Adult onset dominant ataxia (onset usually after age 20)
with retained reflexes and without early slow eye movement or early basal ganglia signs.
.40 6th chromosome (SCA1)
.41 Other locus
.42 locus not known
.43 et seq. Other types and loci

G11.5 Adult onset dominant ataxia with early development of slow eye movements
.50 12th chromosome (SCA 2)
.51 Other locus
.52 Locus not known
.53 et seq. Other types and loci

G11.6 Adult onset dominant Machado-Joseph ataxia. May demonstrate early rigidity, amyotrophy and facial fasciculations
.60 14th chromosome
.61 Other locus
.62 Locus not known
.63 et seq. Other types and loci

G11.7 Other adult onset dominant ataxias
.70 Late onset (usually after age 50) dominant ataxia with retained reflexes
.71 Adult onset dominant ataxia with retinal or optic nerve involvement
.72 Adult onset dominant ataxia with dementia
.73 Adult onset dominant ataxia with periodicity
.74 Et seq. Other adult onset dominant ataxias not identified elsewhere

G11.8 Familial spastic paraplegia
.80 Typical familial spastic paraplegia
.81 Atypical familial spastic paraplegia
.83 Et seq. Other types and loci

G11.9 Ataxia unspecified

In reviewing the issue of classification, Rosenberg (1990) argues that the various subtypes of autosomal dominant OPCA may be examples of a single genetic disease in which the phenotype variability can be attributed to genetic epistasis whereby many other host genes modify the expression and penetrance of the mutant gene. Alternatively each phenotypic variation that may be seen in separate families could be attributed to different mutations. At present there are no known storage products or any primary metabolic clues to indicate a potential molecular basis for the disorder. In the future the discovery of the genotypes will finally settle the issue of classification. Considering these limitations, which are inherent in any existing classification at present, the author has elected to utilize the classification presented in table 3.4 as the framework within which to group the various South African phenotypes. Where appropriate, reference to other classifications outlined in this chapter is also made in the chapters concerning the South African phenotypes.

CHAPTER 4 DEMOGRAPHY

	Page
4.1 Epidemiology of spinocerebellar ataxia	27
4.2 Prevalence of hereditary ataxia in Africa	28
4.3 Demography of the population of South Africa	29
4.4 Demography of the population of the Western Cape	34

CHAPTER 4

DEMOGRAPHY

4.1 EPIDEMIOLOGY OF SPINOCEREBELLAR ATAXIA

This group of disorders is distributed widely in the world. Since the late 19th century different kindreds have been described, in amongst other places, North and South America, the United Kingdom, Europe and Scandinavia as well as India and Japan. They have also been described in islands such as the Azores and Cuba. Nevertheless large scale personal surveys of patients with hereditary ataxias in any one country have been very scarce. The familial ataxias present problems and challenges for any epidemiologic survey. The condition is relatively uncommon and therefore requires surveillance of a large population over many years to accumulate sufficiently large numbers of patients for adequate study. Furthermore case ascertainment in most studies is defined by the clinical assessment of the investigator without reference to diagnostic criteria, which have not been formalized. Such criteria exist for Friedreich's Ataxia but minimal criteria are not agreed upon for the majority of the hereditary ataxias. These difficulties are compounded by the considerable overlap in clinical patterns between the hereditary ataxias and certain other neurologic disorders.

Difficulties with the classification (see 3.3), phenotypic variation, insidious onset and progression (which may require

prolonged follow-up to be certain of diagnosis), are factors which are pertinent to the recording of accurate incidence data. Schoenberg (1978) has reviewed these epidemiological problems and previous prevalence studies. Despite difficulties inherent in comparing one study with another, he argues that most descriptive investigations provide prevalence estimates of less than 6 cases per 100,000 population. This estimate includes early and late onset hereditary ataxias. Higher prevalence figures have been noted in certain communities which are somewhat isolated. Examples of such areas include regions of West Norway, the Azores (Rosenberg, 1978; Coutinho and Andrade, 1978) and Cuba. A prevalence as high as 41 cases per 100,000 population of autosomal dominant ataxia has been recorded in the province of Holguin in Cuba (Orozco et al., 1989). This figure is much higher than in other parts of that country.

4.2 PREVALENCE OF HEREDITARY ATAXIA IN AFRICA

Information concerning the late onset cerebellar ataxias from the African continent is sparse. The results of a field survey in Tunis was published in the French literature (Hamida et al., 1991). These authors analyzed 392 cases of spino-cerebellar degeneration belonging to 188 families and 227 cases of Friedreich's Ataxia and 74 cases of "Pierre Marie type cerebellar ataxia" were identified. They found evidence of clinical heterogeneity as some of these cases had features of peroneal atrophy similar to Charcot Marie Tooth disease while in others there was spastic paraplegia.

Prior to this study there was no data on the spectrum or prevalence of these disorders in South Africa as no population based studies had been done. Philcox et al. (1972) documented a large family of mixed ancestry with late onset cerebellar ataxia in which vestibular dysfunction was an early manifestation. This family has been restudied in detail as part of the present survey.

4.3 DEMOGRAPHY OF THE POPULATION OF SOUTH AFRICA

The Republic of South Africa occupies the southernmost part of the African continent and stretches from the Limpopo river in the north to Cape Agulhas in the south (figure 4.1). The country has an area of 471447 square miles including the previously self administered homeland states (viz.:TBVC homelands: Transkei, Bophuthatswana, Venda and Ciskei) which all lie within the borders of South Africa. Four major ethnic groups are present in South Africa:

a) White persons whose ancestors came from western Europe. These may be further subdivided into two linguistic subgroups: the Afrikaners who are descendants of Dutch, French, and to a lesser degree German forebears and speak Afrikaans; and the English-speaking group. The Afrikaners comprise more than half the white population and the English speaking make up most of the remainder.

b) Black persons who are indigenous to this region of Africa. This group can be further subdivided into four major

ethnolinguistic groups. These are: the Nguni, including the Xhosa, Zulu, Swazi and Ndebele peoples who comprise more than half the Black people of South Africa and live mainly in the eastern coastal regions; the Sotho, found mostly in the central and western areas, and the Venda and Tsonga who comprise the smallest group and are found in the Northern Transvaal.

c) Individuals of mixed ancestry. This population has its roots in the early period of the Dutch East India Company's regime at the Cape of Good Hope. These persons are an admixture of Caucasian, Khoisan (Hottentot and Bushman), Malay (Javanese and Sumatran) and Black ancestry. The majority of this group live in the western part of the Cape province where they comprise the largest ethnic group.

d) Asian individuals whose ancestors are of Indian or Sri Lankan stock. The South African community originated in 1860 when a number of Indians came under contract to work on the Natal sugar plantations. This community grew and the majority still live in Natal province.

South Africa has not escaped the phenomenon of rapid urbanization. Nearly 90% of the White population has been urbanized, 93% of the Asian population, 77,8% of the "Mixed Ancestry" population and nearly 40% of the black population (population census 1985). Black urbanization has accelerated in the last five years following the abolition of influx control laws. The Cape peninsula or greater Cape Town

metropolitan area is one of the six largest urban concentrations in the country (SA yearbook 1990)

The population figures quoted in table 4.1 are according to a mid-year estimate for 1993 released by the central statistical services (5 February 1993). The data refer to the Republic of South Africa according to 1991 boundaries and exclude the TBVC states. The total population of South Africa for June 1993 was estimated at 32,6 million based on the 1991 census.

TABLE 4.1:
POPULATION OF REPUBLIC OF SOUTH AFRICA: MID YEAR ESTIMATE FOR 30 JUNE 1993.

Whites	5 149 000
Mixed ancestry	3 402 000
Asians	1 022 000
Blacks	23 016 000
TOTAL	32 589 000

The estimated population of the TBVC states on census day in 1991 was 6,751,000 (Statistical news release Feb.1993). The annual increase in the black population since 1985 was estimated at 2,78% giving an estimated population of the TBVC states for 1993 of 7,131,600 and a total estimated population of South Africa including the TBVC states for 1993 of 39,720,600.

FIGURE 4.1 MAP OF THE REPUBLIC OF SOUTH AFRICA

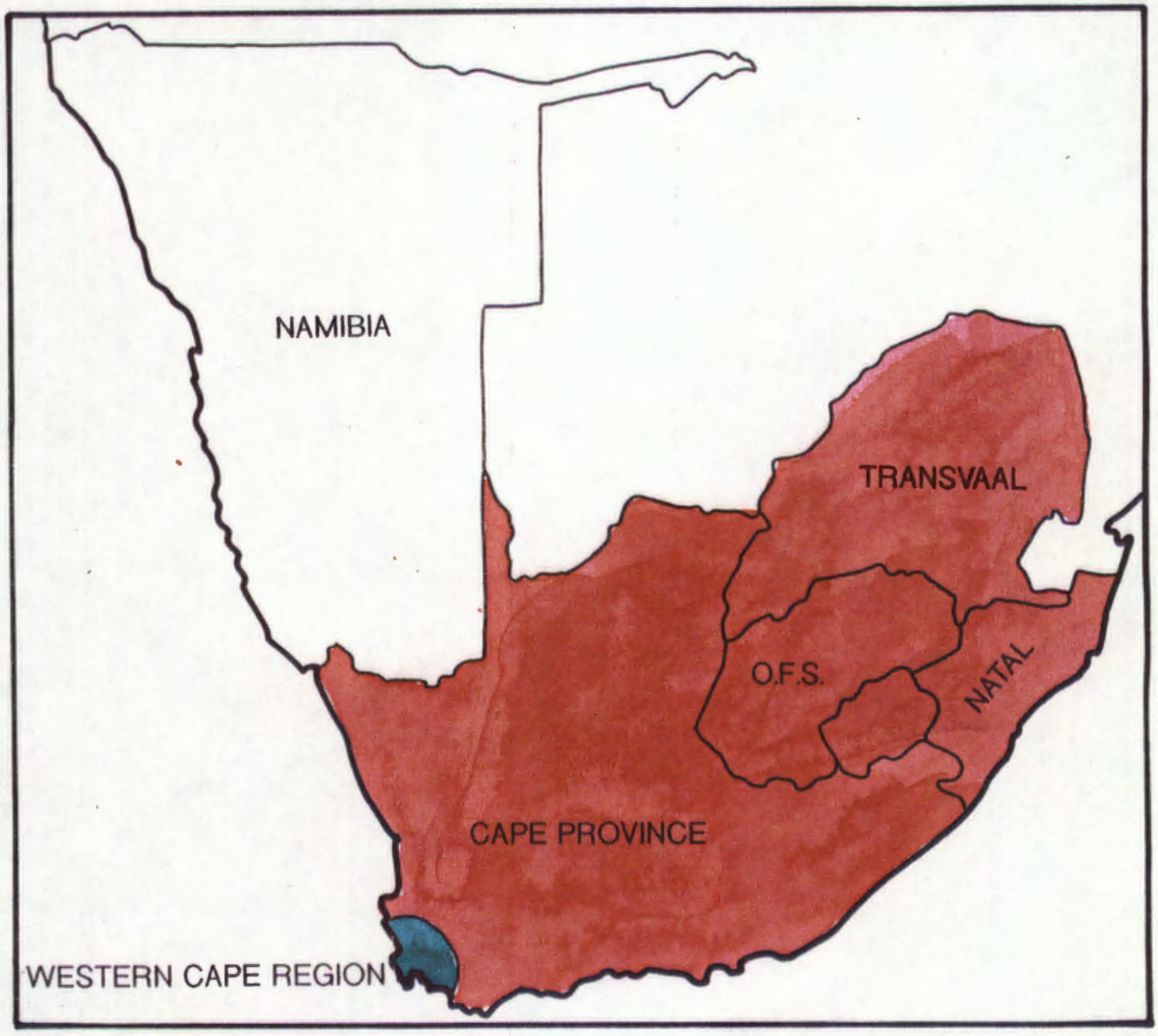
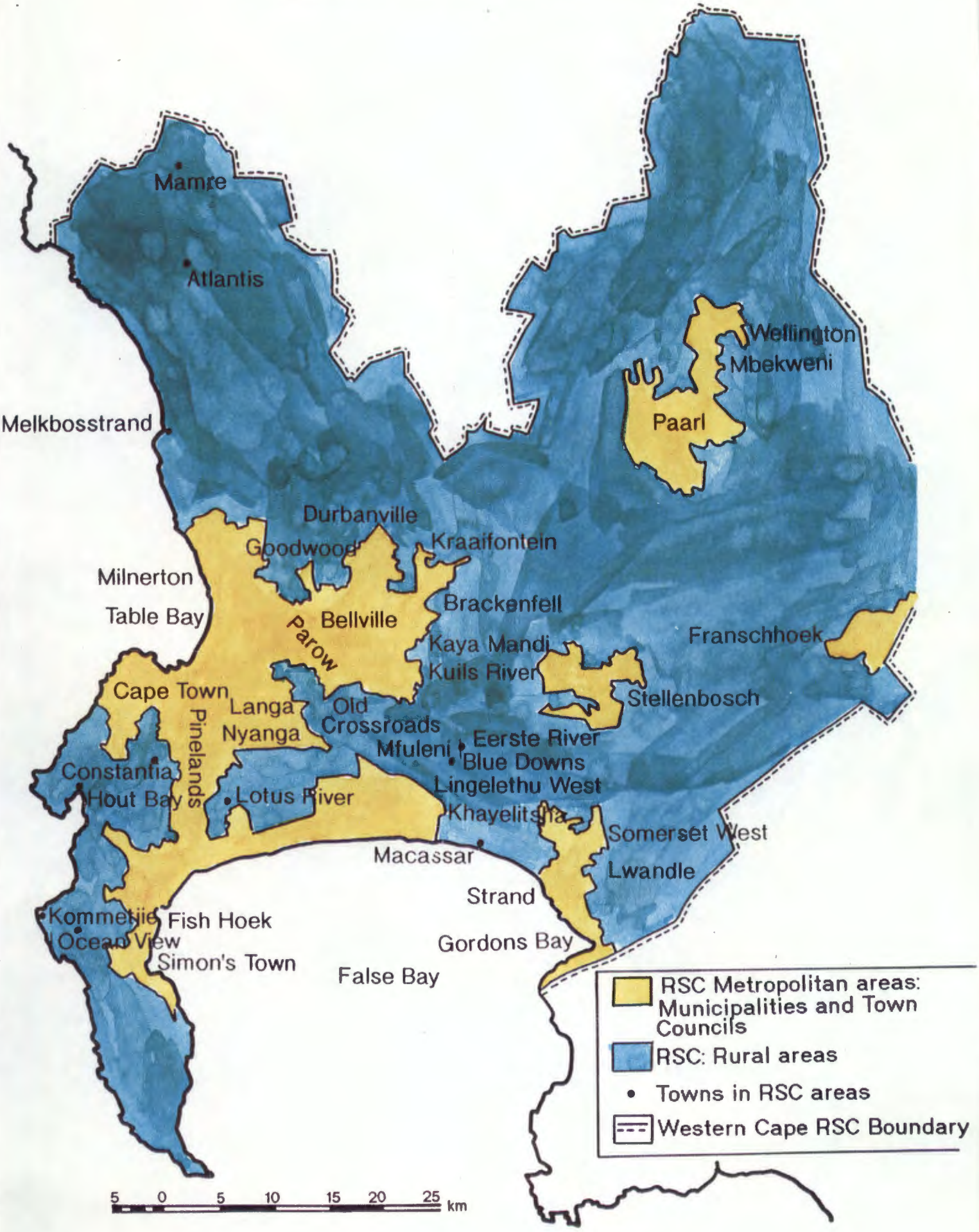


Figure 4.2

WESTERN CAPE REGION

Regional Services Council (RSC) Area



4.4 DEMOGRAPHY OF THE POPULATIONS IN THE WESTERN CAPE

The Western Cape region is illustrated on the map (figure 4.2) and covers an area of 4,260 square kilometers. The area includes those magisterial districts which fall under the administration of the metropolitan state body called the Regional Services Council of the Western Cape. The population of this region based on the 1991 census and released by the City Planners Department of Cape Town is shown in table 4.2 below.

TABLE 4.2:
POPULATION OF THE WESTERN CAPE BY ETHNIC GROUP:

Whites	612 201
Mixed ancestry	1 256 291
Asians	27 057
Blacks	454 610
TOTAL:	2 350 159

The health needs of the population of the Western Cape region is served by several primary care clinics and day hospitals, a number of private and provincial secondary care hospitals and two large tertiary referral academic hospitals. These two hospitals each have a Neurology service and a Clinical Genetics department and have been the major source for case ascertainment for the present study (see 5.1).

SECTION II

PILOT STUDY

Chapter 5 RETROSPECTIVE PILOT STUDY

CHAPTER 5 RETROSPECTIVE PILOT STUDY

		Page
5.1	Background to pilot study	37
5.2	Objectives of the pilot study	37
5.3	Methods	38
5.4	Results of the pilot study	39
5.4.1	Familial cerebellar ataxia	40
5.4.1.1	Sample of affected persons with familial ataxia	40
5.4.1.2	Mode of inheritance	40
5.4.1.3	Phenotype of familial late onset cerebellar ataxia	41
5.4.1.4	Distinct phenotypes	43
5.4.2	Sporadic cerebellar ataxia	45
5.4.2.1	Sample of persons with sporadic ataxia	45
5.4.2.2	Sporadic ataxia phenotype	45
5.4.2.3	Distinct phenotypes of sporadic cerebellar ataxia	46
5.4.2.4	Comment	47

CHAPTER 5

RETROSPECTIVE PILOT STUDY

5.1 BACKGROUND TO PILOT STUDY

In the Western Cape region patients with Spinocerebellar ataxia have been assessed as both inpatients and outpatients in the department of Neurology at Groote Schuur Hospital over many years. The hospital is one of two academic tertiary referral centres which service this area. The collective impression of the neurologists in the department was that the disorder was relatively common in the local population. For this reason a pilot study was undertaken to determine the validity of this impression.

5.2 OBJECTIVES OF THE PILOT STUDY

The objectives of the pilot study were as follows:

i) determine the number of patients with familial and sporadic SCA seen at Groote Schuur Hospital over a 10 year period.

ii) obtain information with regard to the present location and size of affected kindred with a view to a future prospective survey of these families.

iii) document the various phenotypes in this sample of affected persons.

iv) determine the natural history and prognosis in this group.

v) compare the phenotype and natural history of the familial group with individuals with sporadic SCA.

5.3 METHODS

The pilot study was a case finding investigation which took the form of a retrospective analysis of all patients with SCA admitted to Groote Schuur Hospital over a ten year period (1982-1992). Three independent sources were used to ensure optimal ascertainment:

i) Groote Schuur Hospital records: computer retrieval over a ten year period. All patients admitted and discharged from Hospital are summarized and assigned a numerical code according to the diagnosis which is computerized.

ii) Neurology department records. All patients admitted to the neurology wards have a full clinical summary completed on discharge which is kept in the department. Most patients known to have SCA have been assessed as inpatients at least once.

iii) Records of the department of Human Genetics. Since 1972, patients with hereditary diseases have been referred to the department of Human Genetics from sources throughout the country and from within the local population for assessment and genetic counselling. Clinical records detailing the phenotype as well as pedigree are kept in the department. Those pertaining to SCA were accessed.

All patients identified with SCA from the above sources had their medical folders retrieved from the records department. The entire folder was scrutinized including the microfilm containing clinical data and investigations relating the assessment of a patient at the hospital.

5.4 RESULTS OF THE PILOT STUDY

A total number of 67 patients were seen at Groote Schuur Hospital and diagnosed as having SCA. Of these, 29 were familial and 38 were sporadic cases. On careful scrutiny of all available information, 6 of the sporadic cases were found likely to have alternative diagnoses such as multiple sclerosis, alcoholic cerebellar degeneration or cerebrovascular disease. These patients were excluded from this study leaving a total of 32 patients with idiopathic sporadic cerebellar ataxia.

5.4.1 FAMILIAL CEREBELLAR ATAXIA

5.4.1.1 SAMPLE OF AFFECTED PERSONS WITH FAMILIAL ATAXIA

A total of 18 separate families with cerebellar ataxia were identified (families:A,B,D,E,F,G,H,I,J,M,O,Q,S,T,U,V,W, and X; see appendix for pedigrees).

The table below indicates the sex and ethnic groups of the 29 patients with familial ataxia.

TABLE 5.1 ETHNIC GROUP AND SEX OF PERSONS WITH FAMILIAL ATAXIA

Ethnic group	No of patients		
Mixed ancestry	23	(Male : 11	Female : 12)
White	5	(Male : 3	Female : 2)
Black	1	(Male : 0	Female : 1)

5.4.1.2 MODE OF INHERITANCE

The mode of inheritance was clearly autosomal dominant in 9 families (families: A,B,D,E,F,G,H,I,and J) and was probably autosomal dominant in another 4 families (families: M,S,W, and X). In family O the mother was mildly affected and her 3 sons were more severely affected. This observation suggests that she may be a hemizygous carrier of an x-linked recessive disorder or alternatively that the disorder is transmitted in an autosomal dominant manner with variable phenotypic expression. In family Q the mode of inheritance was probably autosomal recessive and in the remaining families (families: T,U, and V) the mode of inheritance could not be determined because of uncertain status of the parents.

5.4.1.3 PHENOTYPE OF FAMILIAL LATE ONSET CEREBELLAR ATAXIA

In 14 of the 18 pedigrees identified, the phenotype was similar to the autosomal dominant cerebellar ataxia type I of the Harding classification. In addition to the cerebellar manifestations other associated features such as pyramidal signs, optic atrophy, ophthalmoplegia, tremor and sensory loss was found in some of the affected individuals. These 14 families are very similar at a clinical level and none were considered to have a unique phenotype in terms of Harding's nosologic criteria.

The symptoms and signs of this of this group of patients are presented in table 5.2 and 5.3.

TABLE 5.2 - SYMPTOMS OF FAMILIAL CEREBELLAR ATAXIA (TOTAL NO 24 PATIENTS)

SYMPTOM	NO OF PATIENTS	PERCENT
Progressive gait disturbance	24	100
Impaired hand coordination	22	92
Dysarthria	20	83
Weakness of limbs	17	71
Dysphagia	8	33
Involuntary movement	6	25
Sphincter disturbance	5	21
Mental disturbance	3	13
Visual impairment	2	8

TABLE 5.3 - CLINICAL SIGNS OF FAMILIAL CEREBELLAR ATAXIA TYPE I

SIGNS	NO OF PATIENTS	PERCENT
Cerebellar ataxia	24	100
Dysarthria	20	83
Pyramidal tract signs	19	79
Abnormal involuntary movement	12	50
Sensory signs	8	33
Dementia	4	17
Generalized muscle wasting	1	4
Eye signs:		
Reduced optokinetic nystagmus	19	79
Nystagmus	8	33
Ophthalmoplegia	6	25
"Staring" eyes	4	17
Optic atrophy	3	13
Ptosis	3	13

The clinical manifestations of this phenotype are discussed in detail in the prospective survey (see chapter 7).

Time to reach dependency:

A total of 6 patients reached a state of severe dependency being completely chair bound. The mean time to reach dependency was 11.5 years (range: 9 - 13 years) Two patients died 10 and 14 years after the onset of their illness.

5.4.1.4 DISTINCT PHENOTYPES

Four families had clinically distinct phenotypes which merited separate consideration and categorization from the group above. In family M, the index patient was an Ovambo female who was referred to Groote Schuur Hospital from Northern Namibia. She presented at the age of 54 years with deteriorating vision and became totally blind within a few years. A gait ataxia developed some years later. She had severe optic atrophy with retinal degeneration as well as cerebellar dysarthria and pyramidal tract signs. She has a young affected son who lives in the Western Cape and attends a special school for the blind. These two affected persons were traced and reassessed prospectively (see 8.3.1)

In family V, the index patient was a white female who presented at the age of 23 years with visual impairment which progressed to blindness. Gait ataxia developed later. Clinically she had pigmentary retinal degeneration, together with cerebellar and pyramidal tract signs. An affected brother had a pigmentary retinopathy and peripheral neuropathy. Both parents had pigmentary retinopathy but were not known to have cerebellar ataxia. This family left the Western Cape region and were not available for prospective evaluation.

In family Q, the index patient was a white male who was noted to be mentally retarded at the age of 14 and in whom mental function progressively deteriorated. Early pyramidal tract signs with weakness and markedly spastic legs with flexion contractures at the knees were noted. There was marked

wasting of the proximal and distal muscles. Cerebellar signs were mild and difficult to interpret in view of the marked spasticity and weakness. Two other siblings and a cousin were subsequently traced and assessed prospectively.

In family O, two brothers, both white males, were assessed. The older brother was found to have a short stature. His symptoms started at the age of 30 years with a mild gait disturbance. He also developed generalized seizures, myoclonic jerks, mild cerebellar signs, nystagmus and a sensory neuropathy in the legs. The younger brother died at the age of 34 years. He had presented with a gait disturbance and weakness in the limbs with deteriorating mental function. He had features of hypothalamic hypogonadism, a sensory peripheral neuropathy, cerebellar ataxia and dysarthria as well as a dementia.

Serum lactate and pyruvate were not measured and a muscle biopsy was not undertaken in either brother. A mitochondrial encephalopathy was considered a possible diagnosis in view of the multisystem involvement. This family was reassessed prospectively and the phenotype is discussed in detail in 8.5.1

5.4.2 SPORADIC CEREBELLAR ATAXIA:

5.4.2.1 SAMPLE OF PERSONS WITH SPORADIC ATAXIA

According to the records 38 patients were initially diagnosed as having sporadic cerebellar ataxia. Careful scrutiny of all data revealed that in 6 of these patients an alternate diagnosis such multiple sclerosis, cerebrovascular disease and alcohol related cerebellar degeneration could best explain their symptoms and signs.

Thirty two patients with sporadic cerebellar ataxia were therefore identified.

The following table indicates the sex and ethnic group of patients with sporadic cerebellar ataxia:

TABLE 5.4 ETHNIC GROUP AND SEX OF PERSONS WITH SPORADIC ATAXIA

Ethnic group	no. of patients	male	female
Mixed ancestry	9	6	3
white	17	3	14
black	6	2	4

5.4.2.2 SPORADIC ATAXIA PHENOTYPE

Twenty one of the 32 sporadic cases had a phenotype consistent with olivopontocerebellar atrophy as described by Dejerine and Thomas in 1900. This phenotype was clinically indistinguishable from the familial group (Harding ADCA type 1). By way of comparison symptoms and signs are presented in Table 5.5:

TABLE 5.5 CLINICAL MANIFESTATIONS OF SPORADIC ATAXIA

Symptoms	**no. of patients**	**%**
progressive gait disturbance	20	95
impaired hand coordination	14	67
speech difficulty	11	52
weakness of the limbs	16	76
involuntary movements	8	38
sphincter disturbance	8	38
visual impairment	8	38
dysphagia	3	14
mental disturbance	3	14
Signs:		
cerebellar ataxia	21	100
dysarthria	13	62
pyramidal tract signs	15	71
abnormal involuntary movements	12	57
sensory deficit	4	19
dementia	6	29
generalized muscle wasting	2	10
eye signs:		
reduced/absent optokinetic nystagmus	7	33
horizontal nystagmus	8	38
ophthalmoplegia	1	5
"staring" eyes	0	0
optic atrophy	4	19
ptosis	2	10

A total of 6 patients reached a state of dependency. The mean time to reach dependency was 8,8 years (range: 3-20 years).

5.4.2.3 DISTINCT PHENOTYPES OF SPORADIC CEREBELLAR ATAXIA

Clinical features such as sensorineural deafness, myoclonus and pigmentary retinal degeneration which seem to run true within families in the inherited group have been also been used as a rubric to define distinctive subgroups within the sporadic group.

Two patients with sporadic cerebellar ataxia had phenotypes consistent with Friedreich's Ataxia and another patient had the features of Friedreich's Ataxia with retained reflexes

(Currier classification - table 3.4). Two patients had features of the "Ramsay-Hunt syndrome" in which cerebellar ataxia and myoclonic jerks are common denominators. This is considered a heterogeneous group of disorders which may be familial or sporadic and associated with other neurologic signs. Within this group are undoubtedly a subgroup who are found to have mitochondrial myopathies when adequately evaluated. In addition to the myoclonus and ataxia, one of these patients had pigmentary retinal degeneration which would favour this diagnosis.

Another group of 4 patients had cerebellar ataxia and sensorineural deafness as well as other evidence of multisystem involvement (viz. dementia, peripheral neuropathy and optic atrophy). A single patient had cerebellar ataxia with athetosis and pigmentary retinal degeneration; it is uncertain what this entity represents. The last patient in this sporadic group with a distinct phenotypes had spastic paraparesis with ataxia.

5.4.2.4 COMMENT

Olivopontocerebellar atrophy (OPCA) is a term first used by Dejerine and Thomas in 1900 when describing two late onset sporadic cases with atrophy of the cerebellar hemispheres, olives and pontine nuclei. Harding has noted that features such as optic atrophy, ophthalmoplegia and retinal degeneration which are found in some cases of hereditary ataxia are seldom if ever reported in sporadic OPCA or parenchymatous cerebellar cortical atrophy (PCCA). This latter

disorder represents a more "pure" cerebellar syndrome and was described by Archambault (1918) and studied again in detail by Marie, Foix and Alajouanine (1922) who thought this to be a separate entity. Harding (1984b) has highlighted many of the difficulties in any attempt to classify this sporadic idiopathic group. The polarization between OPCA and PCCA is unsatisfactory and not particularly useful to clinicians. Many patients with sporadic ataxia have clinical evidence of pathology outside the cerebellum and brainstem. Harding found that the majority of her patients with idiopathic ataxia corresponded to those reported as sporadic OPCA. A smaller group had a predominantly gait ataxia with relatively mild or no ataxia in the upper limbs and a later age of onset. Another small group was identified with a prominent resting or postural tremor. It remains uncertain, however, whether these subgroups represent distinct clinical syndromes.

Some of the individuals with sporadic ataxia in this pilot study almost certainly reflect a hereditary variety. These persons almost certainly represent the only affected member of the family at the time the neurological assessment was done and a number of explanations would account for this phenomenon. If the condition were inherited as an X-linked trait or as an autosomal recessive trait then both parents would be unaffected and the affected person may represent the only affected sibling. This would certainly account for the three unrelated individuals with Friedreich's ataxia. Similarly, those patients with retinal degeneration are almost certainly familial (Harding, 1984). X-linked recessive

cerebellar ataxia with or without spastic diplegia has also been described (Apak, 1989).

The largest group of individuals with sporadic ataxia, however, have a phenotype resembling those reported as OPCA. In the medical literature there are very few reported pedigrees with definite autosomal recessive late onset cerebellar ataxia. Autosomal recessive inheritance is therefore an unlikely explanation to account for all these sporadic cases (Kumar and Timperley, 1988).

A lack of adequate ancestral history and illegitimacy are two factors not infrequently encountered in our local population. This phenomenon could account for some sporadic cases which may be genetically determined. Alternative explanations include unusual genetic mechanisms such as non-penetrance, mitochondrial inheritance patterns and polygenic inheritance. The question of what proportion of sporadic late onset ataxias represent new dominant mutants is clearly relevant in relation to genetic counselling and has been addressed by Harding (1984b) who concluded that the proportion of patients with autosomal dominant cerebellar ataxia who are fresh mutants is probably very small.

It is possible that as yet unexplained environmental factors may be responsible for these sporadic phenocopies but the various possible mechanisms involved in the pathogenesis of this group remains speculative. At present they are best considered within the spectrum of disorders that have been called the "multisystem degenerations".

SECTION III

PROSPECTIVE SURVEY

SECTION III-A: METHOD

Chapter 6 METHODOLOGY OF PROSPECTIVE ANALYSIS

SECTION III-B: RESULTS OF CLINICAL SURVEY

Chapter 7 PROSPECTIVE ASSESSMENT OF AFFECTED FAMILIES

Chapter 8 PROSPECTIVE ASSESSMENT OF EIGHT AFFECTED FAMILIES WITH CLINICALLY DISTINCT PHENOTYPES

CHAPTER 6 METHODOLOGY OF PROSPECTIVE ANALYSIS

		page
6.1	Ascertainment of affected families	52
6.2	Diagnostic criteria	53
6.3	Clinical evaluation	54
	6.3.1 General and neurological examination	54
	6.3.2 Ataxia Severity Score	55
	6.3.3 Optokinetic nystagmus and smooth pursuit eye movements	59
	6.3.4 Assessment of visual function	62
	6.3.5 Assessment of unaffected persons	62

CHAPTER 6

METHODOLOGY OF PROSPECTIVE ANALYSIS

6.1 ASCERTAINMENT OF AFFECTED FAMILIES

An attempt was made to identify all persons in the Western Cape region affected with late onset familial cerebellar ataxia through the following resources:

a) Patients identified in the pilot study utilizing the three sources outlined in 5.1 (viz. Groote Schuur Hospital computer retrieval, Neurology Unit and Department of Human Genetics records).

b) The record system from the Neurology Unit of Tygerberg Hospital.

c) Written requests for patient referral were sent to all seven neurologists on the South African Medical and Dental Council register who are in private practice in the area.

d) Colleague referral from the Departments of Human Genetics and Neurology from the two medical schools and teaching hospitals in the Western Cape.

e) Papers on the clinical and genetics aspects of familial ataxias were delivered at appropriate South African congresses during which appeals for referrals were made.

Day Hospitals and secondary care hospitals were not individually canvassed as it was felt that if any patients were to manifest the characteristic symptoms and signs of this disorder then they would probably be referred to a private neurologist or to the Neurology or Human Genetics Departments of the two academic tertiary hospitals. None of the primary or secondary care hospitals in the area have a Neurology or Genetics service or any neurologists on their staff, making referral of such cases to a tertiary centre almost certain.

All patients were initially interviewed and detailed genealogical data was recorded. Pedigrees were carefully drafted (see appendix for all pedigrees included in this study) and the names and addresses of both affected and unaffected members were recorded for the purpose of prospective recall and assessment.

6.2 DIAGNOSTIC CRITERIA

Only those individuals with late onset familial cerebellar ataxia were included in the study and all were required to have affected relatives. Kindreds in which the majority of affected members were over the age of 20 years when they first had symptoms of the disease, were included in the study. In all such cases progressive cerebellar ataxia was the cardinal clinical manifestation. The presence or absence of other clinical features (ophthalmoplegia, optic atrophy, retinal

degeneration, dementia, amyotrophy of limbs and tongue, extrapyramidal signs eg. rigidity, facial impassivity, choreiform movements and athetosis) as described by Harding (1982a) and noted in the Currier classification, did not preclude inclusion into the study. Any members of a known kindred with familial ataxia found to have an alternative explanation for the cerebellar signs, such as chronic alcoholism, were excluded from the subsequent linkage studies. The congenital and early onset familial cerebellar ataxias of known and unknown aetiology, including Friedreich's ataxia, were excluded from the analysis.

6.3 CLINICAL EVALUATION

All patients referred for the study were examined by a specialist trained in internal medicine and neurology (the author), usually undertaken in the Department of Neurology at Groote Schuur Hospital, but sometimes in their homes or a local rural clinic. In each case, a thorough medical history was obtained and each patient was evaluated according to a set protocol, a copy of which is included in the appendix.

6.3.1 GENERAL AND NEUROLOGICAL EXAMINATION

The physical examination was performed using standard clinical procedures. A detailed appraisal of each of the body systems, with a full neurological examination, was done by the author. If there was uncertainty relating to the presence of early signs of the disease, or if the diagnosis was in question in any way, then patients were reviewed in the Groote Schuur

Hospital Neurology Unit so that all relevant information could be augmented by evaluations from colleagues.

6.3.2 ATAXIA SEVERITY SCORE

Currently there is no universally accepted scale or scoring system to grade the severity of ataxia and in the past individual researchers have devised their own methods of evaluating it. In September 1993, the Ataxia Research Group of the World Federation of Neurology elected a sub-committee to address this issue. This group (author included) intend to devise a standardized scoring system that is comprehensive and will be widely and reliably applied by clinical researchers in different countries. In this study, the author tested co-ordination using the following well known clinical tests:

1. Finger/nose test
2. Repetitive and alternating hand movements
3. Copy drawings
4. Heel-shin test
5. Toe/finger test
6. Truncal sway
7. Balancing on one leg

In all instances both left and right limbs were individually tested. The tests are briefly described below:

1. Finger/nose test: the person was asked to hold an arm outstretched and then touch the tip of his nose with the tip of his index finger and then touch the end of the examiner's finger which was held at arms length away from the person. This action was repeated several times, after which the examiner moved his index finger from place to place whilst the

person's finger was en-route to it. Care was taken to ensure that the person fully extended the arm to reach the target and did not adduct the upper arm against the trunk for support. The examiner evaluated this manoeuvre for dysmetria and intention tremor.

2. Repetitive and alternating movements: The person was requested to tap repeatedly the dorsal aspect of one hand (held stationary) with the palmar aspect of the other from a height of approximately 40cm. He/she was then requested to pronate and supinate the forearm and repeatedly slap the dorsal aspect of one hand (held stationary) with the dorsal and palmar aspect of the other hand. The person was then asked to increase the speed of the manoeuvre. The rhythm, amplitude and force of the repetitive tapping movements and the individual's ability to make the alternating movements was evaluated and scored.

3. Copy drawings: the person was asked to copy two diagrams (i.e. a spiral and a 5 pointed star - see appendix), without resting thee pen-holding hand on the writing surface, and with the upper arm abducted from the trunk.

4. Heel/shin test: The test was performed with the individual in the supine position. He/she was requested to raise one leg and then place the heel on the knee of the resting leg and then slide the heel down the anterior tibial surface of the resting leg towards the ankle. On reaching the ankle joint the leg was again raised in the air to a height of approximately 40cm and the action was repeated. The action was evaluated for dysmetria and ataxia (causing the heel to shift off the anterior tibial surface).

5. Toe/finger test: This test is similar to the finger/nose test; the individual lay in the supine position and was requested to repeatedly raise one leg with the big toe aiming to touch the examiner's finger tip which was held approximately 40cm above the resting position of the leg.
6. Truncal sway: The person was observed sitting erect with the arms folded in front of the chest, and also in the standing position. The presence and degree of truncal sway was assessed and scored.
7. Balancing on one leg: The person was requested to stand on one leg and maintain balance without holding onto adjacent objects (the examiner was positioned close to the patient to provide support in the event of the individual being unable to maintain balance).
8. Intention tremor: a separate score was assigned for the severity of the intention tremor depending on the performance of tests numbers 1, 3, 4, and 5.

The scores for these clinical tests were assigned as follows:

1 = normal

2 = mild impairment

3 = moderate impairment

4 = severe impairment

5 = unable to perform the task

Gait: The person was requested to walk in a straight line for a distance of approximately 6 metres or more and then turn around and walk back. This was repeated a few times if necessary. Gait was assigned and scored as follows:

1 = normal;

2 = person has subjective sensation of unsteadiness, but no definite ataxia observed by the examiner;

3 = objective evidence of mild gait ataxia;

4 = moderate gait ataxia;

5 = severe ataxia (walks with a stick or requires support);

6 = chair bound.

The scores for the gait and the other tests outlined above were summated for a global ataxia severity score and 5 categories were defined (table 6.1).

TABLE 6.1 ATAXIA SEVERITY SCORE

9 - 10	=	normal
11 - 21	=	mild ataxia
22 - 26	=	moderate ataxia
27 - 31	=	moderately severe ataxia
> 32	=	severe ataxia

6.3.3 OPTOKINETIC NYSTAGMUS AND SMOOTH PURSUIT EYE MOVEMENTS

Optokinetic nystagmus is easily demonstrated in normal persons. It consists of nystagmus which is elicited by repetitive visual stimuli moving through the visual field, or, conversely when a person moving past a series of stationary objects refixes vision. There is a slow and a rapid phase to the nystagmus. The slow phase tracks the moving target and the fast phase is a saccadic movement in the opposite direction.

OKN is tested in the horizontal and vertical planes but is less well sustained in the vertical plane. A metallic optokinetic tape painted with alternating black and white bands spaced at 3cm intervals was used to test this phenomenon. The person directed gaze at the tape, which was held approximately 30cm from his/her eyes and was slowly moved in the horizontal plane to the right and then to the left. Normally, there is a slow movement in the direction of the movement of the bands and a rapid, "refixation" movement in the opposite direction. When the tape is moved up or down in the vertical plane the nystagmus is vertical. Results were then graded from 0 (absent) to 3+(normal).

Optokinetic nystagmus was introduced as a clinical tool by Barany in 1921 but knowledge of the mechanisms underlying the phenomenon and all the anatomic substrates involved in its production is incomplete. It would appear that OKN is a phenomenon engaging many areas of the brain and is a product of a visual input and an oculomotor output (Carmichael et al.,

1954). Both horizontal and vertical OKN are very sensitive indicators of oculomotor dysfunction (Davidoff, 1966). Lesions in the deep parietal lobe cause a deficit in OKN when movement is towards the side of the lesion. The brain stem areas act as integrators and final common pathways for the optokinetic response. Discrete lesions involving the pontine nuclei (ie. dorsolateral, lateral, and dorsomedian pontine nuclei, which represent a crucial relay between cerebral cortex and the cerebellum in the control of eye movements) cause an impairment of OKN and smooth pursuit eye movements (Johnston et al., 1992; Gaymard et al., 1993). The slow phase velocity of the optokinetic response is characteristically impaired in individuals with brainstem or cerebellar lesions (Yamada et al., 1991). The optokinetic response overrides many voluntary eye movements and vestibular nystagmus and can also be used to estimate visual acuity in infants (it is present within a few months after birth) and may be useful establishing the presence of vision in patients who are hysterically blind or malingering. In a study of 150 patients with spinocerebellar degeneration, an abnormal optokinetic response correlated with the duration of the disorder (Mizuno and Yamane, 1993).

Pursuit eye movements stabilize on the fovea the images of an object moving slowly in the environment. Moving targets can be followed smoothly and accurately (with eye velocity about equal to target velocity provided the target velocity is less than about 50 degrees per second and, for periodic targets, the frequency is less than about 1 hertz) (Miller, 1985). The

cerebellum plays an important part in the generation of smooth pursuit eye movements and OKN (Buttner, 1989; Pierrot-Deseilligny et al., 1990). The same neural elements are responsible for an initial jump in slow phase eye velocity during constant velocity stimulation and for the optokinetic response (Buttner, 1989). Impaired smooth pursuit movements are associated with lesions in the hemispheres, cerebellum or brainstem pathways, but may also be induced by drugs (eg.barbiturates, phenytoin), anxiety and fatigue (Newman, 1993).

Smooth pursuit eye movements were tested by asking the individual to follow a target moving slowly and smoothly across the field of vision, with the head held still. Normally, the subject should do this both smoothly and precisely. Inability to maintain smooth pursuit results in interruption by microsaccades (cogwheel pursuit) (Bogousslavsky and Meienberg, 1987).
The range of ocular movement and binocular co-ordination of motility was evaluated while testing smooth pursuit movement. Normally, both eyes move conjugately into all extremes of gaze. A normal full horizontal movement conceals the limbus (the border of the cornea and sclera) under the medial and lateral canthus. Vertically, upgaze should reach at least 30 degrees (Newman, 1993).

6.3.4 ASSESSMENT OF VISUAL FUNCTION

Affected members from any kindred who had visual impairment were examined and assessed by specialists in ophthalmology at Groote Schuur Hospital. Visual acuity and formal computerized visual field perimetry were tested in these individuals and the ophthalmologists performed the relevant investigations (eg ERG and fluorescein angiography) if indicated.

6.3.5 ASSESSMENT OF UNAFFECTED PERSONS

An experienced and qualified nursing sister with training in human genetics assisted the author in locating affected and unaffected members at risk in the different families (figure 6.1). This nursing sister is well versed in the recognition of both early and late manifestations of the disorder. During two visits to a peripheral clinic which was attended by over sixty members from a single large kindred, the author was assisted by two other doctors trained in clinical genetics who helped with the evaluation of unaffected members (figure 6.2). Persons with any relevant symptoms or signs were then referred to the author for appraisal.

FIGURE 6.1 CLINICAL ASSESSMENT OF AN UNAFFECTED FAMILY MEMBER An unaffected person (family B) is assessed for impaired balance and gait at a clinic.

FIGURE 6.2 THE "TEAM" EN ROUTE TO A PERIPHERAL CLINIC

On a visit to a rural clinic, the author was assisted by 2 other doctors trained in clinical genetics, a psychologist, an occupational therapist, 2 nursing sisters, and a laboratory technician.

THE METHODOLOGY OF THE DIAGNOSTIC IMAGING IS DETAILED IN CHAPTER 9.

THE METHODOLOGY OF THE NEUROPHYSIOLOGICAL TESTING IS DETAILED IN CHAPTER 10.

THE METHODOLOGY OF THE MOLECULAR LINKAGE STUDY IS DETAILED IN CHAPTER 11

SECTION III B: RESULTS OF CLINICAL SURVEY

CHAPTER 7 PROSPECTIVE ASSESSMENT OF AFFECTED FAMILIES

		Page
7.1	Symptomatology	67
7.1.1	Gait disturbance	68
7.1.2	Upper limb incoordination	70
7.1.3	Speech disturbance	70
7.1.4	Muscle cramps	70
7.1.5	Weakness	71
7.1.6	Urinary symptoms	71
7.1.7	Vision	71
7.1.8	Cognitive decline	72
7.2	Clinical signs	72
7.2.1	Gait	74
7.2.2	Limb ataxia	74
7.2.3	Dysarthria	78
7.2.4	Pyramidal tract signs and muscle weakness	78
7.2.5	Abnormal involuntary movements	79
7.2.6	Dysphagia and upper airway dysfunction	80
7.2.7	Sensory impairment	82
7.2.8	Ocular signs	83
7.2.9	Dementia	85
7.2.10	Evolution of the phenotype	87
7.3	Time to reach dependency	90

7.4 Deaths 90

7.5 Minimal prevalence 90

7.6 Conclusions 92

CHAPTER 7

PROSPECTIVE ASSESSMENT OF AFFECTED FAMILIES

A total of 18 families were identified (ethnic groups: mixed ancestry 9, white 7, black 2). In 10 of these families the phenotype was similar, and the remaining 8 had clinically distinct phenotypes.

A total of 40 affected persons from the 10 families were prospectively assessed. The manifestations of the disorder in these persons from the 10 families with the same phenotype are reviewed in detail in this chapter and the 8 families with clinically distinct phenotypes are discussed in chapter 8. Many of the unaffected first degree relatives in each family were also assessed, often repeatedly, for signs of the disorder. The pedigrees, which were carefully constructed are illustrated in the appendix. Nine of these families were of mixed ancestry and the remaining family was white.

7.1 SYMPTOMATOLOGY

The mean age of onset in ten families was 30.7 years with a range of 16 years to 48 years. In 90% of affected persons, the symptoms started before the age of 40 years. The duration of the illness varied from less than 1 year to 20 years with members showing varying degrees of severity at time of the prospective assessment. The presenting symptomatology in this group is shown in table 7.1. The symptoms are not correlated with the duration of the disorder.

Table 7.1 SYMPTOMS OF FAMILIAL LATE ONSET CEREBELLAR ATAXIA IN FAMILIES WITH THE SAME PHENOTYPE

Symptom	No of patients	Percentage
Gait disturbance	39	98
Frequent falls	23	58
Impaired hand co-ordination	33	83
Abnormal involuntary movements	12	30
Speech disturbance	35	88
Dysphagia	13	33
Weakness in the legs	25	63
Weakness in the arms	18	45
Visual impairment	7	18
Cognitive deterioration	7	18
Sphincter disturbance	13	33
Muscle cramps	13	33

The symptomatology of the disorder, illustrated with anecdotal reports, is reviewed below. A formal account of the clinical signs follows in 7.2.

7.1.1 GAIT DISTURBANCE

Gait disturbance was the earliest and most troublesome symptom in the majority of persons. Initially affected individuals noted the gait disturbance to be intermittent. A slight stagger or veering to one side would occasionally occur with normal walking between these episodes. Sometimes family members or work colleagues would be the first to observe or remark on this phenomenon.

A young man (family C), who was later assessed to be mildly affected at the age of 34, had trained in karate for several years and at the age of 25 first noticed that when he had to kick above a certain height he would lose his balance. Despite vigorous training, this did not improve and only

months later did he become aware of some unsteadiness while running and subsequently while walking. A number of affected individuals reported that in the initial stages, the severity of the gait ataxia would fluctuate from day to day ("I sometimes walk straight and then skew like a drunkard and I can't run because of the feeling that I am going to fall"). Several people reported that walking was always more unsteady after a period of inactivity (eg. after being sedentary for more than 15 minutes). Once the gait ataxia was well established, individuals frequently compared their walking to that of a drunken person. Many individuals reported that their gait was much more troublesome when walking on uneven surfaces, when physically tired, or when standing on moving vehicles or climbing steps; walking uphill was often easier than walking downhill. One man (family A), who had been ataxic for 20 years commented: "My walking is unsteady, as if I did not lift my foot high enough to take the step".

A tendency to fall frequently accompanied the onset of the gait disturbance. This problem occurred predominantly in the early stages of the disorder in individuals with mild ataxia who had not yet restricted their physical activities. With progression, individuals became more aware of persistent gait ataxia and tended to be more cautious, restricting their physical activities and falling less frequently. As the ataxia progressed, falling became more frequent until the person became wheelchair bound. Two individuals sustained major fractures following falls in the advanced stages of the disorder.

7.1.2 UPPER LIMB INCOORDINATION

Dysarthria and incoordination in the upper limbs invariably occurred some months or even years after the initial symptom. The onset and awareness of ataxia in the upper limbs depended on the fine motor skills and needs of the particular individual. One man (family A) worked as a draftsman on a computerized drawing board and first became aware of the problem when he observed that he took longer to use the keyboard and his production dropped ("I was on the carpet because I failed to meet deadlines"). Changes in handwriting and clumsiness with the tendency to drop items were not infrequently an early symptom of limb ataxia.

7.1.3 SPEECH DISTURBANCE

A change in the rhythm and fluency of articulation was often noted by family members or friends of affected individuals. They described speech as being slurred or mumbled and this was predictably more evident when the individuals had to speak on the telephone. One young lady commented "I have to speak slowly because I can't pronounce the words properly".

7.1.4 MUSCLE CRAMPS

Muscle cramps, occurring especially at night or during periods of inactivity, were not an infrequent complaint. They did not respond to treatment with quinine and were most troublesome in the thigh and calf muscles. This observation was made by 12 individuals with the disorder varying in severity from the mild to severe stages.

7.1.5 WEAKNESS

Although muscle fatigue in the legs was a frequent complaint, objective weakness on clinical testing was only evident in 6 individuals all of whom had moderately severe or severe ataxia. It is likely that affected persons often incorrectly attributed the symptom of incoordination to one of weakness in the limbs. Similarly, in the 18 people who complained of weakness in the upper limbs only 5 had objective weakness on clinical examination. Twelve individuals complained of abnormal involuntary movements such as tremor, titubation or chorea.

7.1.6 URINARY SYMPTOMS

Eleven people with moderate to severe disease complained of urinary urgency (often passing urine seven or more times per day) with episodic urge incontinence. The latter usually occurred when individuals were unable to get to the toilet speedily because of the ataxic gait. Sexual function was usually preserved even in more advanced stages of the disorder. Only 2 affected individuals complained of impaired ability to obtain an erection.

7.1.7 VISION

Six individuals complained of some impairment of vision but this was not severe and did not restrict their activities of daily living. Dysphagia was reported by 13 affected members and was usually a symptom which occurred late in the course of the illness. However, 3 individuals developed the symptom

early and their ataxia score was noted to be in the mild category of severity. The dysphagia was worse with soft foods and liquids and there was a tendency to nasal regurgitation and aspiration in the late stages. A barium swallow was undertaken on one affected person with dysphagia; this revealed a marked oesophageal motility disorder to be the cause of the symptom.

7.1.8 COGNITIVE DETERIORATION

An awareness of cognitive deterioration usually occurred late in the course of the illness and was more often reported by unaffected close family members. Impaired concentration and forgetfulness were the first symptoms of the dementia. However, 1 individual who had been symptomatic with ataxia for 5 years (ataxia score: moderate) had worked as a cashier in her husband's store. She had to stop working because she found that she would forget the price of items commonly purchased and the names of long-standing customers; she struggled to count and calculate the amounts of money for transactions .

Psychosocial problems were encountered in both affected and non-affected individuals and will be discussed in detail in chapter 12.

7.2 CLINICAL SIGNS

The clinical signs present in the affected individuals from the ten families with the same phenotype are presented in table 7.2. In each individual the degree of ataxia was

assessed and assigned a score of severity as outlined in chapter 6.

TABLE 7.2
CLINICAL SIGNS OF FAMILIAL LATE ONSET SPINOCEREBELLAR ATAXIA

Clinical signs	No of patients	Percentage
Gait ataxia	40	100
Upper limb ataxia	38	95
Dysarthria	37	93
Pyramidal tract signs	34	85
Weakness in the limbs	10	25
Muscle wasting	8	20
Sensory impairment	9	23
Dysphagia	7	18
Abnormal involuntary movements	16	40
Dementia	10	25

TABLE 7.3
OCULAR SIGNS IN FAMILIAL LATE ONSET SPINOCEREBELLAR ATAXIA

Clinical signs	No of patients	Percentage
Reduced or absent optokinetic nystagmus	38	95
Loss of smooth pursuit	36	90
Optic atrophy	6	15
Ophthalmoplegia	12	30
Staring eyes	8	20
Ptosis	5	13
Nystagmus	8	20

TABLE 7.4
SEVERITY OF ATAXIA AT PROSPECTIVE ASSESSMENT

Category of severity	No of persons	Percentage
Mild	11	27
Moderate	9	23
Moderately severe	9	23
Severe	11	27
Total	40	100

7.2.1 GAIT

The disorder usually presents with a gait ataxia. The gait looses its usual rhythmicity and becomes jerky and irregular. Affected individuals initially walk on a narrow base with a tendency to take unequal steps which may veer off to the side of the line of direction. Arm-swinging movements also become jerky and irregular and an affected individual may develop titubation while walking. Abrupt turning may evoke postural instability with a stagger and difficulties maintaining equilibrium are evident. Tandem walking (viz: heel of one foot in line and in contact with toe of the other foot) accentuates the gait deficit and reveals problems with walking on a narrow base or the tendency to fall to one side. These typical phenomena were described in great detail in the Croonian lectures on the Clinical Symptoms of Cerebellar Disease by Sir Gordon Holmes in 1922 (Holmes, 1922). As the gait deteriorates the person becomes more unsteady and tends to walk on a wider base to secure better balance (Figure 7.1). With further progression assistance will be required with walking, either by holding onto another person or by grasping furniture and adjacent walls for support. Finally, the complex sequence of movements required for gait disintegrate to a degree where the person is no longer able to walk and becomes confined to a wheelchair.

7.2.2 LIMB ATAXIA

Months or even years after the gait disturbance begins, ataxia in the upper limbs develops with the characteristic intention tremor, dysmetria and typical past pointing. Rapid repetitive

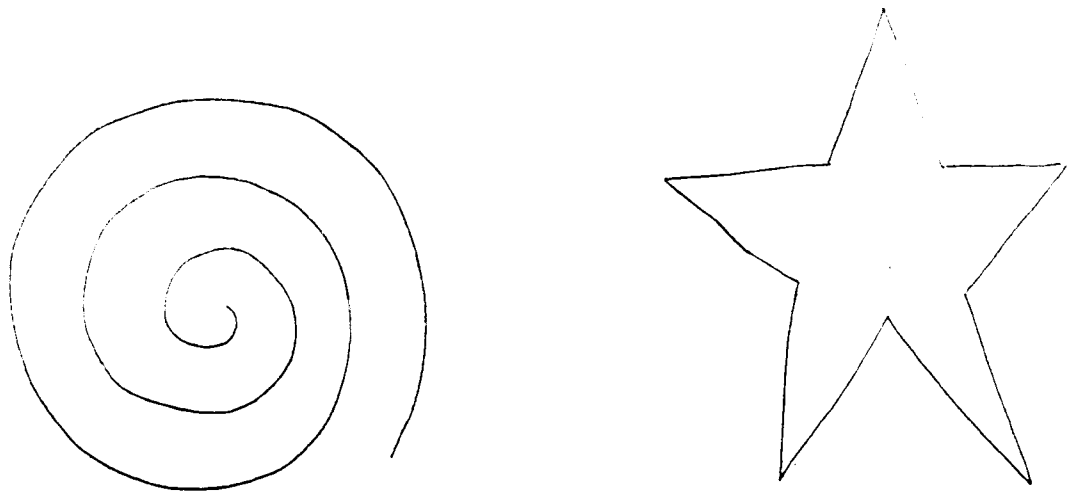
movements are slowed, with a change in the force, timing and amplitude of successive movements such as hand tapping. Dysdiadochokinesia (ie a derangement of the function of arresting one motor impulse and substituting one that is diametrically opposite) is evident on testing alternate movements of the hands which are performed with increasing clumsiness and slowness. Irregularity of the rate and range of movements is prominent, pronation and supination being separated by intervals which vary constantly. Handwriting becomes more jerky and illegible as upper limb ataxia progresses. The dysmetria (inability to properly direct or limit voluntary movement) is clearly visible when asking affected individuals to copy a diagram such as a five cornered star or spiral without resting the hand or arm on the writing surface. Examples from different individuals are illustrated in figure 7.2. Similarly these individuals were unable to make repeated dots with a pen within a circle with the hand held above the paper (figure 7.3).

FIGURE 7.1 AN AFFECTED PERSON WITH A BROAD BASED GAIT

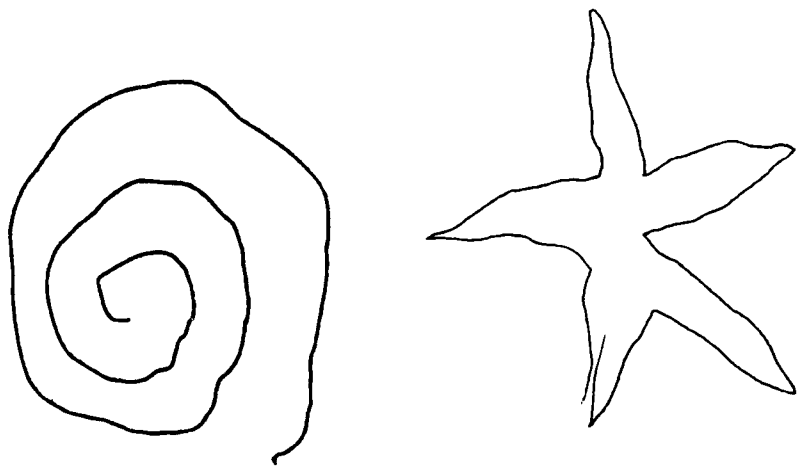
A 28 year old affected member (family A) standing on a broad base for better balance.

FIGURE 7.2 (a, b, c, d) COPIED DIAGRAMS - EXAMPLES BY INDIVIDUALS WITH MILD TO SEVERE ATAXIA

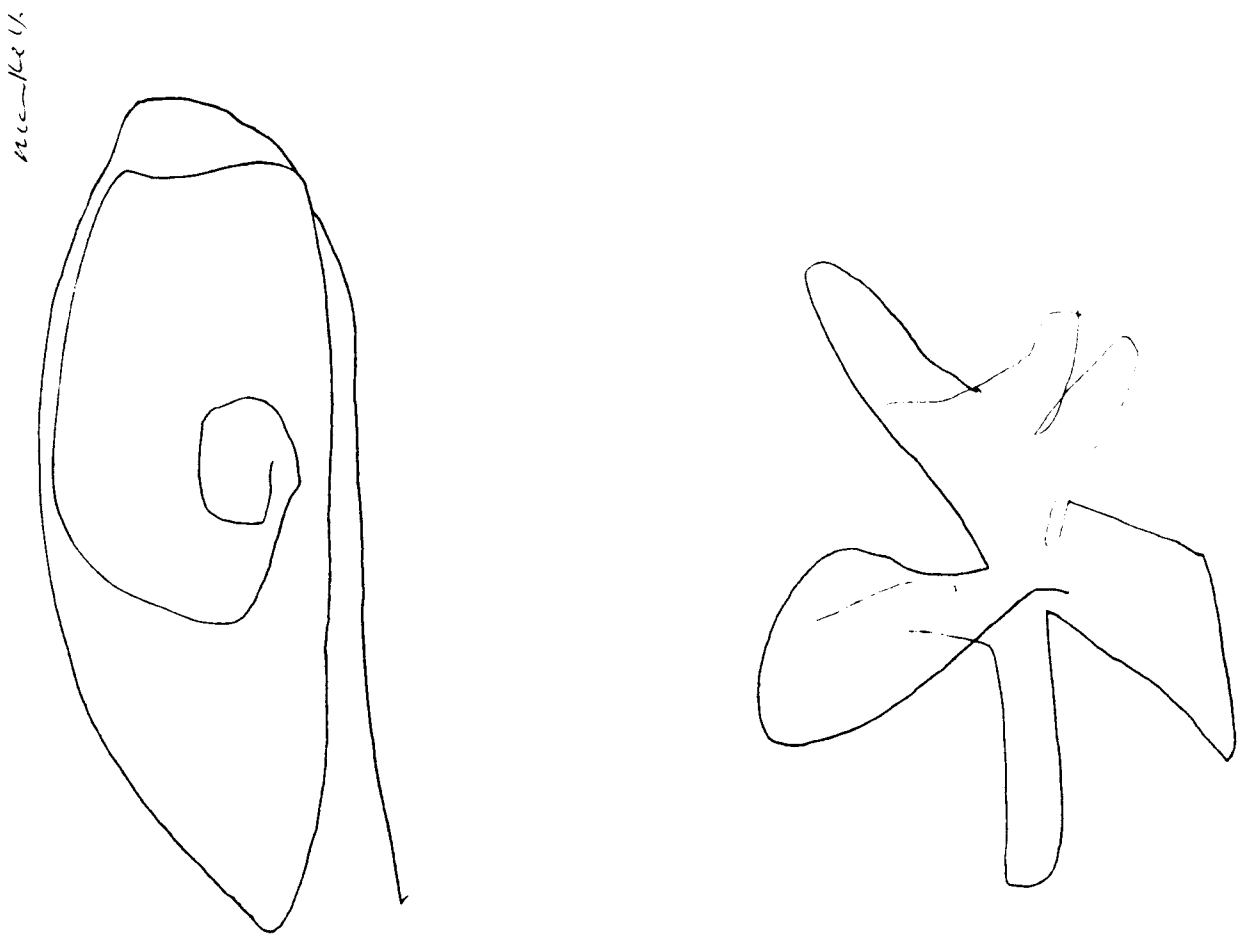
a) Examiner's diagrams (spiral and star)



b) Diagrams by a person with mild ataxia



c) Diagrams by a person with moderate ataxia



d) Diagrams by a person with severe ataxia

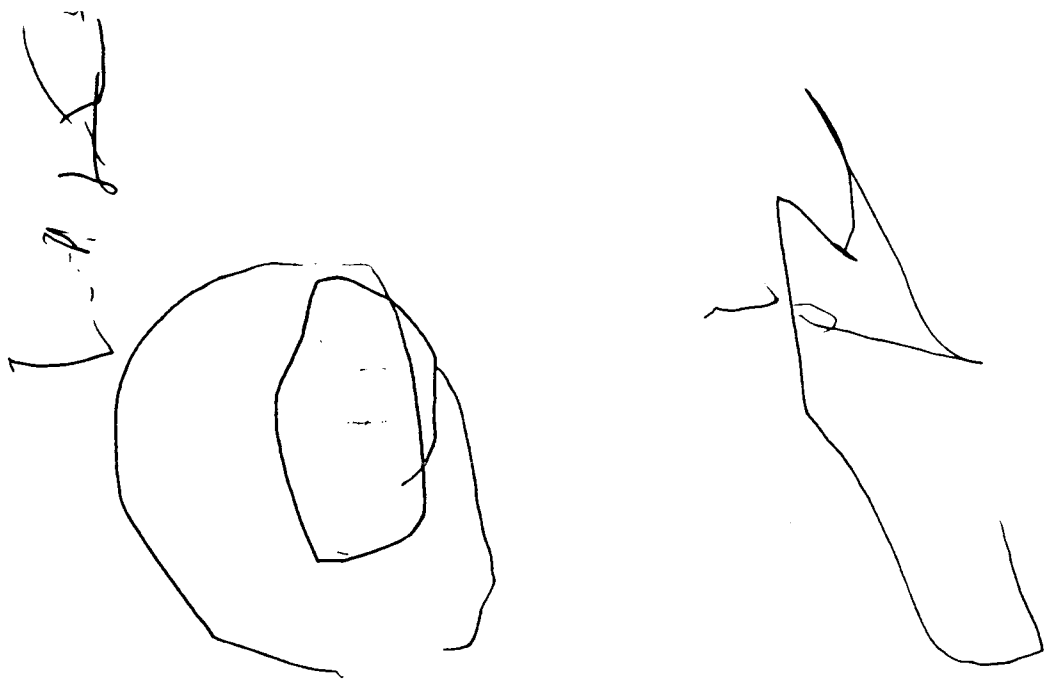


FIGURE 7.3 CIRCLE AND DOT TEST

Examples by 2 affected persons who were unable to make repeated dots within a circle with the hand held above the paper (some of the dots are beyond the circumference of the circle).

7.2.3 DYSARTHRIA

Dysarthria was a common clinical finding. The character of speech was both staccato and slurred with loss of normal cadence. Rapid repetition of syllables (eg la-la-la, go-go-go) accentuated the dysarthria. Dysarthria usually evolved months to years after the appearance of the gait ataxia. It was observed in all affected persons except five individuals who had mild ataxia scores. The slow monotonous quality of the voice gradually became more indistinct and unintelligible.

7.2.4 PYRAMIDAL TRACT INVOLVEMENT AND MUSCLE WEAKNESS

Signs of pyramidal tract involvement (viz. abnormally brisk reflexes, extensor plantar responses, spasticity) were present in 27 affected individuals and was first evident in the lower limbs. They usually occurred in persons with moderate to severe ataxia scores and not in those with early signs. Only 10 individuals, all with moderately severe to severe ataxia,

had evidence of mild proximal muscle weakness (grade 4+/5, British Medical Research Council grades) and the remainder had normal muscle power. In the advanced stages of the disorder eight people had profound weight loss with diffuse muscle wasting. Fasciculations were seen in the calf muscles in one individual.

7.2.5 ABNORMAL INVOLUNTARY MOVEMENTS

A postural tremor of the head or trunk was observed in 10 individuals. This rhythmic rocking movement, which was either forward and backwards or from side to side, occurred at a rate of several times per second and was often more noticeable when the subject stood upright. This sign is well described in individuals with disease of the midline cerebellar zones and has little localizing value (Gilman, 1985). In addition to the characteristic intention tremor, a static or rest tremor was evident in 7 people with ataxia. This usually involved the limbs (except for one person with tremor of the lips) and was asymmetrical and intermittent in some individuals. This clinical sign was also well recognized in the early literature (Holmes, 1922). A single individual with severe ataxia of early onset developed choreiform movements of her fingers late in the course of her illness. She has impaired position sense in the extremities and this may well have accounted for these movements.

7.2.6 DYSPHAGIA AND UPPER AIRWAY DYSFUNCTION

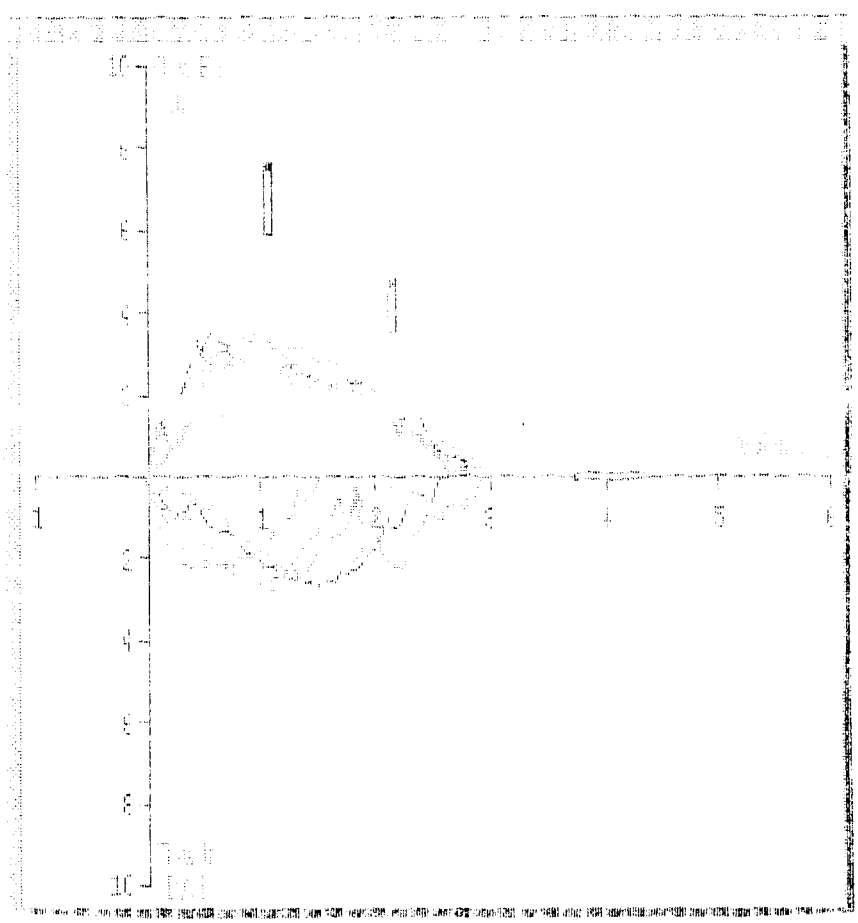
Persistent dysphagia was present in 7 individuals. This was associated with nasal regurgitation during swallowing, and in the later stages of the illness with recurrent aspiration pneumonia. The cough reflex was often weak. Four of the seven individuals have since died. A barium swallow carried out on one of the individuals (family A, IV-19) showed a marked oesophageal motility disturbance. One affected individual (family A, IV-20) was admitted to hospital complaining of great difficulty swallowing food, and bouts of repeated choking and coughing after swallowing. He was treated for bilateral aspiration pneumonia and was noted to have a very weak cough reflex which contrasted with well preserved power in the limbs. Despite the severe ataxia he was still able to walk in his home using the walls for support. After the pneumonic illness had resolved, full pulmonary function tests were undertaken in order to elucidate the problem as little has been written on the subject (Schiffman, 1992). This man had no family history of asthma and he denied any wheezing or episodic shortness of breath. He previously smoked 5 cigarettes per day for 5 years but had not smoked for the past 6 years. The results of lung function studies are listed in table 7.5 below.

TABLE 7.5
LUNG FUNCTIONS ON AN INDIVIDUAL WITH RECURRENT ASPIRATION PNEUMONIA

Spirometry	Actual value	Predicted value
FEV_1	2480	3400
FVC	2942	4280
FEV_1/FVC %	84.3	78
PEF	211	421
PIF	156	280
Lung volumes		
IC	1080	
ERV	1300	
SVC	2220	4280
FRC	5560	3280
RV	4260	1840
TLC	6640	6120
RV/TLC %	64.2	
MIPS	40	124
MEPS	35	233

FIGURE 7.4 FLOW-VOLUME LOOP OF AN AFFECTED PERSON WITH RECURRENT ASPIRATION PNEUMONIA

[Flow Ex. = flow during expiration
Flow In = flow during inspiration
l/s = litres per second
l = litres]



Lung function tests showed some evidence of gas trapping with slightly reduced volumes but these were difficult to interpret (particularly the MIPS and MEPS) because of technical difficulties secondary to the patient's impaired muscle coordination. The flow-volume loop is shown in figure 7.4 and this is remarkably similar to that shown in the paper of Schiffman (1992).

On fibre-optic laryngoscopy, the naso and oropharynx as well as the vocal cords appeared normal anatomically. The vocal cords closed well on phonation. During coughing, the cords leaked air throughout the attempted adduction and there was obvious global glottic and supraglottic incoordination in that the explosive action necessary for cough could not be generated. The glottis appeared to be adequately protected by the epiglottis during swallowing. There was no detectable intercostal or diaphragmatic weakness; this observation was confirmed by the spirometric values which did not reveal a major drop in the values in the erect and supine positions. The major clinical problem was the clearing of secretions as well as a loss of glottic protection.

7.2.7 SENSORY IMPAIRMENT

Impairment of joint position sense and vibratory sensation in the distal lower limbs was documented in 9 individuals, most of whom had severe ataxia scores. Not unexpectedly this feature was detected less frequently in the upper limbs (4 individuals) and was not thought to be a significant causative factor for disability. Two individuals had evidence of

peripheral neuropathy with a distal sensory loss to touch and pinprick. Nerve conduction studies will be discussed in chapter 10.

7.2.8 OCULAR SIGNS

Reduced or absent vertical and horizontal optokinetic nystagmus was the most common ocular manifestation of the disorder. This tended to be an early clinical sign but was not observed clinically in 2 individuals with mild gait ataxia. Reduced smooth pursuit with the individual using short saccadic movements to track a moving target occurred in 80% of affected individuals. Eight individuals had fine horizontal nystagmus (rapid phase to the side of gaze) on lateral gaze which was often not sustained. A striking feature was the "staring" look of the eyes observed in eight patients. Eyelid retraction with a rim of sclera visible above the iris, and also, possibly, reduced blinking and small random lateral eye movements accounted for this appearance (figure 7.5). This clinical sign, although seldom mentioned in the literature, has been observed in other families with ataxia (Jampel et al., 1961, Healton et al., 1980). Ocular signs evident with advanced illness included supranuclear ophthalmoplegia (12 persons), optic atrophy (6 persons) and partial ptosis (5 persons). Failure to sustain upward gaze was the earliest sign of ophthalmoplegia. Those individuals with optic atrophy did not complain of any visual deficit.

Many of the affected persons with moderate and severe ataxia also exhibited facial impassivity. The decrease in the normal facial expressions was not matched by detectable facial muscle

weakness (figure 7.5a and 7.5b). These individuals could frown, blow up their cheeks and purse their lips and did not demonstrate the typical facial apraxia observed in Huntington Disease (Harper, 1991).

FIGURE 7.5 (a, b, c) THREE AFFECTED PERSONS WITH "STARING EYES"

a)

b)

c)

7.2.9 DEMENTIA

A decline in cognitive function was recorded in 10 individuals. As many people were assessed in their own homes or at peripheral clinics, formal psychometric testing was not undertaken for logistic reasons. Furthermore 9 of the 10 individuals had severe or moderately severe ataxia with dysarthria, rendering formal testing difficult or impossible to execute. The assessment of a dementia was done by interview of first degree relatives, and during clinical history-taking and by bedside testing for short-term memory including mini-mental examination where appropriate. Memory impairment was recorded in 9 of these individuals. Two persons had a severe mood disorder for which they required hospitalization. Behavioral disorders (eg aggression, disinhibition) were a major problem for the family of four persons. Only one affected person who had previously worked as a schoolteacher, was formally tested and found to have an full-scale IQ of 86 following admission to hospital for

delusional ideation. This score was considered to be below an expected score required to perform her previous profession with competence.

A factor which hindered the accurate assessment of a cognitive decline in these circumstances was the uncertainty with regard to the previous level of intellectual ability and cognitive performance, particularly in those individuals with a rudimentary formal education. Furthermore, severely affected individuals with motor and speech disabilities are frequently not expected or required to manage their own affairs and their relatives often do not test or rely on their memory ability. Relatives may thus be unaware of (and therefore under-report) any cognitive decline.

Of note were two other affected persons (family A, IV-61, IV-34), both still working at the time of prospective analysis, who complained of forgetfulness. The first worked as a store planner and complained of difficulty recalling certain familiar items which he felt he ought to have remembered. The second, worked in the accounts department of a firm and observed that he was no longer as quick with numbers as he used to be and was having to use a calculator more frequently. Both individuals had no difficulty performing the mini-mental examination and other basic tests of short-term memory. These complaints may reflect early changes in cognitive function but it is conceivable that anxiety relating to their ataxia in the work environment may have contributed to some impairment of concentration. Formal psychometric testing was not done. At

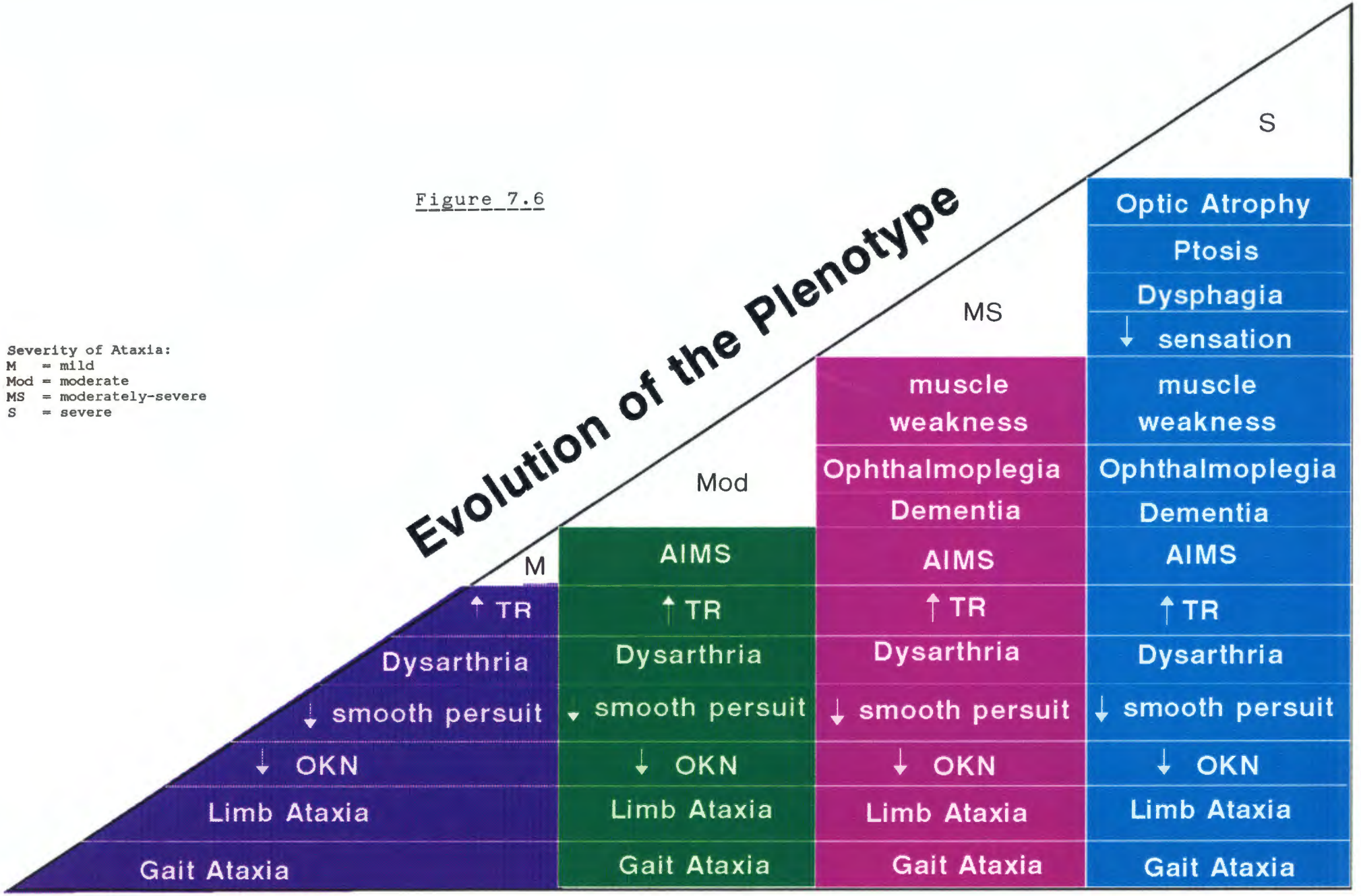
the time of last assessment, both were coping adequately in their work and home environments.

7.2.10 EVOLUTION OF THE PHENOTYPE

Although much has been written about phenotypic variability and the wide range of clinical signs which may be present even within a single family (Pedersen, 1980; Diaz et al., 1990), a recognizable pattern emerges when individuals are followed up serially as the disorder progresses . Longitudinal descriptions of the evolving phenotype are, however, scant in the literature. Reports document the frequency and range of clinical signs encountered within a family, but seldom relate these findings to the duration or severity of the ataxia. In order to address this problem affected individuals were divided into four groups (table 7.4) depending on the severity of ataxia. As the rate of progression varies considerably within a given family (younger onset often tending to a more rapid course), the ataxia severity score was used to chart the evolution of the disorder rather than the duration of disease, which is a more subjective and variable parameter. Figure 7.6 documents the clinical signs present at different stages of ataxia severity for this particular group of individuals with the same phenotype. A particular clinical sign had to be present in more than one third of individuals within each category of severity to be included in the appropriate segment of the diagram, which graphically depicts the evolution of the disorder in these individuals. A recent study, of 6 Italian families with autosomal dominant ataxia, also demonstrated that clinical manifestations appeared

concordant when patients with the same disease duration were compared (Spadaro et al., 1993).

Figure 7.6



Severity of Ataxia:
M = mild
Mod = moderate
MS = moderately-severe
S = severe

7.3 TIME TO REACH DEPENDENCY

At the time of the last assessment a total of 9 people had become dependent and wheel-chair bound. The mean time to reach a state of dependency was 10.1 years (range: 6 years to 13 years). There were however, other individuals in this group who had been symptomatic for longer and were not yet dependent. One man (family A, III-18) had developed the first symptoms at the age of 35, and though he had moderately severe ataxia (score 27) twenty years later, he was still able to walk with the aid of a stick.

7.4 DEATHS

Five affected individuals died during the course of this study. All had severe or moderately severe ataxia scores at the time of their last assessments. The mean age at the time of death was 39.2 years with a range of 26 years to 47 years. The mean duration of the illness in these individuals was 11.4 years with a range of 9 to 19 years.

7.5 MINIMUM PREVALENCE

The frequency of a disease may be expressed in terms of the prevalence (ie. total number of affected persons in a defined population at a specific time) or the incidence (ie. total number of affected persons newly ascertained in a given time period). A number of factors are pertinent to the recording of accurate incidence data (eg. the insidious onset of the disorder which may require prolonged follow-up to be certain

of the diagnosis) and for this reason prevalence figures are more widely quoted in the few epidemiologic studies of familial ataxia (see 4.1) in the literature. An earnest attempt was made in this study to identify all affected persons with late onset ataxia in the Western Cape region (see 6.1). Factors such as incomplete referral, however, and the reluctance of some affected persons (who are aware of the familial nature of the condition and that there is no curative treatment at present) to present themselves for medical evaluation, has almost certainly prevented complete ascertainment. Nevertheless, a minimum prevalence rate of the occurrence of the disorder in the Western Cape region of South Africa was calculated for the December 1993 population statistics (see 4.4). Prevalence was calculated according to the following formula:

$$\text{Prevalence} = \frac{A \times 10^6}{\text{population}}$$

A = the total number of living affected persons on the prevalence day.

The number of living affected persons with late onset ataxia, including all the different phenotypes (as described in chapters 7 and 8) was 58. The minimum prevalence was 24.68 per million for the population of the Western Cape.
The prevalence of familial ataxia in the various ethnic groups within the region is presented in Table 7.6 below:

TABLE 7.6 MINIMUM PREVALENCE OF FAMILIAL ATAXIA IN THE WESTERN CAPE POPULATION

Ethnic group	No. of persons	Prevalence x 10^{-6}
White	13	21.24
Mixed ancestry	41	32.64
Black	4	8.80

The highest prevalence was observed in the group which were of mixed ancestry (total of 9 families including the 2 largest families A and B. see appendix)

7.6 CONCLUSIONS

The phenotype described in this chapter would meet the criteria for classification as Adult onset dominant ataxia with retained reflexes (Currier/Subramony classification) or Autosomal dominant cerebellar ataxia type 1 (Harding). Although the minimum prevalence data indicate that familial late onset ataxia is an uncommon disorder in the region, a total of 163 individuals (each with unaffected parent) from these families carry a 50 % risk (autosomal dominant inheritance only) of developing the disorder. The problems pertaining to the high risk status of these individuals will become the greatest challenge facing the resources of the Neurogenetics clinical service in the future.
Autosomal dominant spinocerebellar ataxia is a devastating disease and there is an urgent need to develop an accurate and reliable presymptomatic test. If a gene carrier could be identified prior to the onset of the illness, appropriate counselling might be given with regard to the 50% risk to the offspring, although this approach is not without ethical

issues. In addition, with the availability of modern techniques, such as chorionic villus biopsy and the polymerase chain reaction, prenatal diagnosis would allow the option for abortion of an affected foetus.

Studies to determine the genotype of this group will be discussed in detail in chapter 10.

CHAPTER 8 PROSPECTIVE ASSESSMENT OF EIGHT AFFECTED FAMILIES WITH CLINICALLY DISTINCT PHENOTYPES

page

8.1 Late onset cerebellar ataxia without dysarthria and ocular signs 96

8.1.1 Phenotype of family K 96

8.1.2 Discussion of family K 98

8.2 Very late onset cerebellar ataxia with depressed reflexes 99

8.2.1 Phenotype of family L 99

8.2.2 Discussion of family L 100

8.3 Autosomal dominant ataxia with macular degeneration 100

8.3.1 Phenotype of family M 100

8.3.2 Discussion of family M 102

8.4 Autosomal dominant ataxia with macular degeneration and slow eye movements 104

8.4.1 Phenotype of family N 104

8.4.2 Discussion of family N 107

8.5 Cerebellar ataxia and hypogonadism 109

8.5.1 Phenotype of family O 109

8.5.2 Discussion of family O 111

8.6 Cerebellar ataxia, optic atrophy and deafness 114

8.6.1 Phenotype of family P 114

8.6.2 Discussion of family P 117

8.7 Cerebellar ataxia, mental retardation, motor neurone syndrome and macular degeneration 120

8.7.1 Phenotype of family Q 120

8.7.2 Discussion of family Q 122

8.8 Spastic paraparesis with ataxia and dystonia 125

8.8.1 Phenotype of family R 125

8.8.2 Discussion of family R 126

8.9 Conclusions 127

CHAPTER 8

PROSPECTIVE ASSESSMENT OF EIGHT AFFECTED FAMILIES WITH CLINICALLY DISTINCT PHENOTYPES

In the previous chapter, 10 families with the same phenotype have been discussed. A further 8 families with diverse phenotypes form the subject of this chapter. A total of 17 affected persons from 8 families were prospectively assessed. Six of these families were white and the remaining two families were black. These 8 kindreds had phenotypes which were clinically distinct from each other and from the phenotype described in chapter 8. These represent rare disorders and for the sake of clarity the phenotype of each family is discussed separately in paragraphs 8.1 to 8.8 of this chapter.

8.1 LATE ONSET CEREBELLAR ATAXIA WITHOUT DYSARTHRIA AND OCULAR SIGNS

8.1.1 PHENOTYPE OF FAMILY K

Two individuals (family K) with very late onset cerebellar ataxia were assessed. The pedigree is illustrated in the appendix. The proband (II-6) developed a gait disturbance at the age of 63 years. Eight years later her gait had worsened but she had developed no new symptoms. On clinical examination she had gait ataxia (ataxia score 22 : moderate) with only mild incoordination in the upper limbs. She had brisk tendon reflexes but normal tone and power in all limbs

with equivocal plantar responses. Optokinetic nystagmus and smooth pursuit eye movements were both present, possibly slightly reduced. After eight years of symptoms her speech did not have the typical characteristics described in 7.2.3. She was followed up over a three year period and at the time of her last assessment at the age of 70 years, her daughter commented that she thought that her mother's memory had become impaired. She tended to forget certain appointments and had, for example, asked the family what they had done on a particular day when she had in fact been with them during that period. A mini-mental test score was 29/30 at that time. None of her four children (aged between 33 to 40 years) had any symptoms of the disorder.

A younger brother (II-9), aged 61, developed similar symptoms at the age of 48 years. He was assessed 13 years later at the age of 61 years. He remembered that initially he was unsteady when walking on uneven surfaces and that he had fallen a few times when "there was no reason for falling". He complained that "my walking has definitely got worse but it is a very slow process". Clinical examination again revealed a gait ataxia without upper limb ataxia. Biceps and tendon reflexes were brisk and the plantar responses extensor. Speech was normal and the ocular signs were subtle (minimally reduced optokinetic nystagmus). Although he complained that he was a little more forgetful than in previous years, this did not interfere with his life in any way (mini-mental examination 30/30). All of his children were asymptomatic (ages 25 to 36 years). On clinical examination both the proband and her

brother did not have any abnormal involuntary movements, dysphagia, ophthalmoplegia, optic atrophy or sensory disturbance. Neither drank excessive amounts of alcohol. An older brother (II-1) had developed similar symptoms at the age of 50. A CT scan was done and he was told that he had "problems with his cerebellum". He subsequently died at the age of 58 years of a cardiac condition. Both parents were deceased (father died aged 76 and mother at age 58) and neither had any gait disturbance prior to their deaths. None of the paternal or maternal aunts and uncles or cousins of the affected individuals had had a similar disorder.

8.1.2 DISCUSSION OF FAMILY K

The affected members of this family developed a late onset gait ataxia with very slow progression. The typical cerebellar type of dysarthria and ocular signs described in chapter 7 were not evident. Mild forgetfulness occurred late in the course of the disorder. The ataxic gait with relatively unimpaired limb coordination suggests anterosuperior vermal cerebellar involvement (Gilman, 1982). The mode of inheritance is consistent with an autosomal recessive pattern. However, taking account of the very late onset of the disorder, autosomal dominant inheritance cannot be excluded as it is conceivable that the mother of the affected individual (I-2) may have died prior to developing any symptoms. The phenotype described in this family can tentatively be classified as "adult onset recessive ataxia with retained reflexes, locus not known" (Currier/Subramony classification).

8.2 VERY LATE ONSET CEREBELLAR ATAXIA WITH DEPRESSED REFLEXES

8.2.1 PHENOTYPE OF FAMILY L

The proband in family L (III-2) developed symptoms of a slowly progressive cerebellar syndrome at the age of 63 years. The initial symptom was a gait disturbance with frequent falls and this was followed by dysarthria. Twelve years later at the age of 75 she was assessed prospectively and found to have a moderate, gait ataxia (ataxia score 24) with mild incoordination in the upper limbs. Cognitive function was normal and her speech was slurred. She had rotatory nystagmus on lateral gaze and optokinetic nystagmus was absent. Smooth pursuit movements were reduced. Muscle power and tone were normal but the tendon jerks were depressed in the upper limbs and absent in the lower limbs. Plantar responses were flexor and sensory examination was normal.

A younger sister (III-3) had developed a similar gait disturbance at an earlier age and died at the age of 64 years. She apparently had a more severe gait disorder but additional details were not available. Their mother (II-2) had a similar disorder and died in 1947 at the age of 58. Attempts to trace her medical records were unsuccessful. The maternal grandparents (I-1,I-2), both died at the age of 78 and were apparently unaffected, but there was insufficient information to be certain about their neurological status. Two younger siblings, a sister and a brother were apparently unaffected

and died at the age of 54 years and 39 years from cardiac failure and multiple myeloma respectively.

8.2.2 DISCUSSION OF FAMILY L

Only the proband was alive and available for prospective assessment. The mode of inheritance appeared to be autosomal dominant. The full spectrum of the phenotype could not be reliably ascertained as no other affected relatives were available for evaluation. The most notable clinical features in the proband were the late onset, the slow course of the gait ataxia with dysarthria and reduced or absent tendon reflexes. It is uncertain whether the phenotype described above represents a distinct entity or whether it is a variant of the more commonly encountered phenotype described in chapter 7.

8.3 AUTOSOMAL DOMINANT CEREBELLAR ATAXIA WITH MACULAR DEGENERATION

8.3.1 PHENOTYPE OF FAMILY M

At the age of 34, the index case (family M, I-2) started to develop progressive visual loss. Three years later she developed the first symptoms of gait ataxia followed by dysarthria, incoordination in the upper limbs, muscle cramps and urinary frequency.

At the age of 48 years, she had severe visual impairment being able to see hand movements only. Fundoscopy revealed a maculopathy with retinal degeneration and optic atrophy.

External ocular movements were normal but optokinetic nystagmus and smooth pursuit movements could not be tested because of poor vision. She had a cerebellar type of dysarthria and signs of pyramidal tract involvement in all four limbs (viz increased tone, abnormally brisk reflexes and an extensor plantar response on the left). Sensory examination was normal. Her gait was ataxic and broad-based. She had incoordination in the upper limbs with a typical intention tremor. Nerve conduction studies in the arms and legs did not reveal any electrophysiologic evidence of a sensorimotor peripheral neuropathy.

The eldest of her seven children (II-1) has a similar disorder. He spent several years at a local school for the blind before leaving the area. He had been assessed at one of the local teaching hospitals (Tygerberg Hospital - Neurology Unit) before he left the region. He was apparently well until the age of 13 when he started developing progressive visual loss in both eyes followed by gait ataxia. Five years after the onset of his symptoms, his vision had deteriorated to the level where he was only able to count fingers at 50 cm. Fundoscopy showed macular degeneration with a non-pigmentary retinopathy. Like his mother, he had limb and gait ataxia and pyramidal tract signs in his legs. The remaining six siblings were said to be asymptomatic, but could not be assessed for early signs of the disorder as they did not live locally.

8.3.2 DISCUSSION OF FAMILY M

The phenotype in this family is similar to that designated as " Adult onset dominant ataxia with retinal or optic nerve involvement" (Currier/Subramony classification) or "Type II autosomal dominant cerebellar ataxia with retinal degeneration" (Harding classification). Harding (1984a) has reviewed earlier reports and argues convincingly that the association of hereditary ataxia and retinal degeneration constitutes a phenotype which is clinically and genetically distinct from autosomal dominant cerebellar ataxia type I. Molecular studies in this family which support this contention of syndromic identity are discussed in chapter 11.

The combination of ataxia and retinopathy has been reported as concordant within families to a greater extent than the "cerebellar ataxia plus" syndromes (Harding, 1984a).
In nearly all the families reported with this association, every member has had retinal degeneration. The age of onset is usually earlier than type I ataxia (see chapter 8) and the disorder may develop in the first five years of life (Carpenter and Schumacher, 1966; Colan et al., 1981). Most affected people have the onset of symptoms in their second and third decades and symptoms seldom begin after the age of 40.

Visual deterioration is characteristically the first symptom and usually precede the ataxia by several years. The degenerating retina may show pigmentary changes which seem primarily to affect the macula (Halsey et al., 1967); in some reported cases, however, the periphery is more severely

affected (Carpenter & Schumacher, 1966). Optic atrophy is common in these persons (Weiner et al., 1967). Visual acuity is severely reduced and many patients are blind by the fourth decade of life. Ophthalmoplegia has also been described in combination with retinal degeneration in a number of families but was not present in all affected persons (Jampel et al., 1961; Halsey et al., 1967; Weiner et al.,1967; Harding 1982). Dysarthria and pyramidal tract signs are well described in affected individuals with this phenotype (Halsey et al., 1967; Harding, 1984a). Variability of clinical features and pathological manifestations within some families has been reported (Colan et al., 1981; To et al., 1993).

The inheritance pattern in family M appears to be autosomal dominant and although the six younger siblings were asymptomatic, these individuals have not been formally assessed. In this context, it is noteworthy that electroretinographic changes may be present in affected family members who are entirely asymptomatic and have a normal ophthalmologic evaluation (To et al., 1993). These authors emphasize the usefulness of electroretinogram in providing early evidence of retinal degeneration. In their experience the earliest change in the retina of affected individuals was reduction of amplitudes in the isolated cone responses, indicative of a cone dysfunction.

Ocular histopathology studies in families with cerebellar ataxia with retinal degeneration show similar findings in the different families (Weiner et al., 1967; Ryan et al., 1975; To

et al., 1993). In the study of To et al., the inner and outer segments of the photoreceptive layer of the retina and macula showed diffuse degeneration affecting both rods and cones. The photoreceptor degeneration involved the entire retina, but was more severe in the macula.

Molecular studies (chapter 11) in this South African family support the contention that this phenotype is clinically distinct from that described in chapter 7 (viz. autosomal dominant cerebellar ataxia type I Harding).

8.4 AUTOSOMAL DOMINANT CEREBELLAR ATAXIA WITH MACULAR DEGENERATION AND SLOW EYE MOVEMENTS

8.4.1 PHENOTYPE OF FAMILY N

The proband (family N, IV-3; figure 8.1) developed slowly progressive visual impairment at the age of 24 years. This symptom was followed by a gait ataxia and impaired hand coordination. At the age of 28 years, the visual acuity was severely reduced (6/60 on the left and finger movements only in the right eye). Fundoscopy revealed a "bulls-eye" maculopathy (figure 8.2). A striking feature was the very slow eye movements; random and voluntary eye movements (saccades) were smooth but very slow in all directions. She could not abduct the eyes fully on extreme lateral gaze (figure 8.3). Titubation with mild but definite ataxia of gait and limbs (ataxia score 21) was observed. She was not

dysarthric but had difficulty with rapid repetition of short syllables (eg la-la-la).

Electroretinogram results were consistent with a cone dystrophy (unrecordable cone responses; rod responses normal). CT scan showed gross cerebellar atrophy. Serum concentrations of lactate, Vitamin E and alphafetoprotein were all normal. Aminoacid levels and organic acid profiles were also normal. According to the proband, her mother, aged 70 years, started developing progressive visual impairment with gait ataxia at the age of 66 years. She lives in a remote rural area of the Transkei and was not available for clinical assessment. However, her cousin (IV-16) who developed similar symptoms at the age of 26 years, was assessed (figure 8.1). In this person, visual symptomatology also preceded the gait disturbance. At the age of 28 years her visual acuity was reduced (6/60 on the left and 12/60 on the right) and fundoscopy showed a maculopathy. Eye movements were very slow in all directions. She had titubation and a moderate gait and limb ataxia (ataxia score 25). The rest of the examination was normal apart from absent ankle jerks.

FIGURE 8.1 PROBAND AND COUSIN (FAMILIY N)

The proband (IV-3) and her cousin (IV-16) stand and walk on a broad base.

FIGURE 8.2 "BULLS-EYE" MACULOPATHY

Photograph of the retina of the proband of family N demonstrating a "bulls-eye" maculopathy.

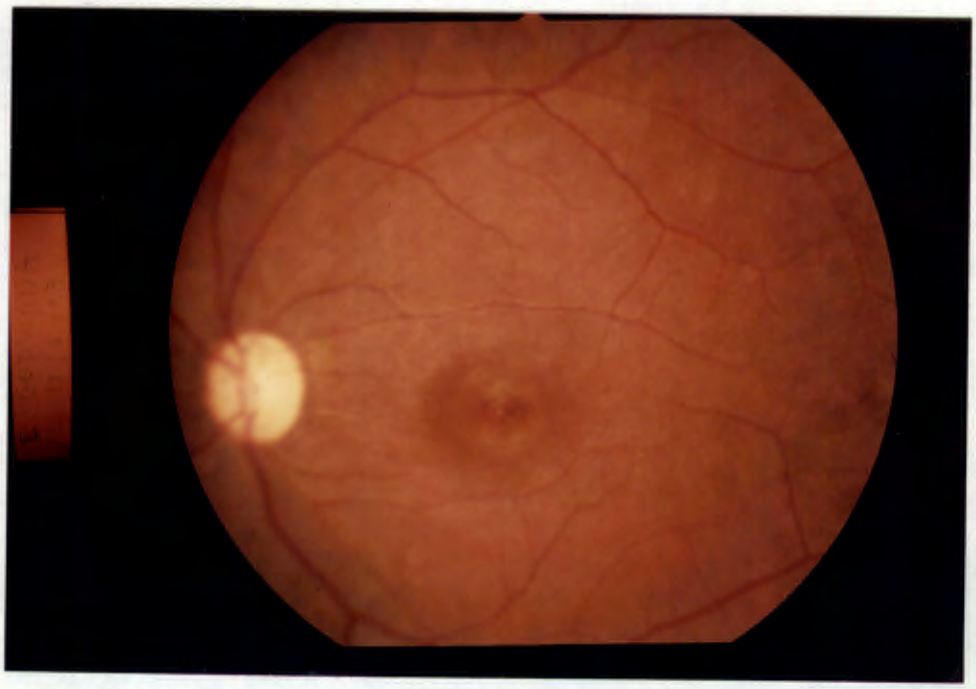


FIGURE 8.3 IMPAIRED LATERAL GAZE

The proband is attempting to gaze to the left and is unable to adbuct the left eye fully.

8.4.2 DISCUSSION OF FAMILY N

The mode of inheritance is autosomal dominant in this family. The separation of this kindred from the family described in 8.3.1 was based on the presence of very slow eye movements. This may well prove to be a tenuous basis for sub-division. Wadia (1971,1977,1984) described 37 patients from 23 Indian families with very slow eye movements and suggested that these families form an identifiable subgroup. In these Indian families, the disorder began with a slowing of the horizontal random and voluntary eye movements through the full range. The slowing of the eye movements gradually became more obvious in all directions. Limitation of gaze in the terminal range of

horizontal and vertical movement occurred and a staring expression of the eyes was observed in some affected people. Individuals used compensatory head movements for looking at objects. Electro-oculographic recordings demonstrated that the slowing was restricted to saccadic movements, although this may be difficult to distinguish clinically (Kulkarni, 1975). The available histopathology from the Indian families falls within the spectrum of olivopontocerebellar atrophies. The phenotype is characterized by the presence of cerebellar ataxia, typical slow eye movements and clinical or subclinical affection of the spinal lower motor or sensory neurones. Wadia (1984) suggests that this phenotype represents a recognisable recurrent clinico-pathological pattern in the Indian population. However, none of the affected persons from the Indian families had macular degeneration or severe loss of vision. Harding (1984a) has commented that slow eye movements have been observed in families with hereditary ataxias of many types and she questioned if the group of patients with slow eye movements has a separate syndrome.

Although family M and family N both have cerebellar ataxia with macular degeneration and severe visual impairment, the slow speed of the eye movement in the two affected members of family N is a distinguishing clinical feature. For this reason family N cannot be readily classified under the existing schema because those families classified as having slow eye movements do not have macular degeneration and vice versa.

8.5 CEREBELLAR ATAXIA AND HYPOGONADISM

8.5.1 PHENOTYPE OF FAMILY O

The propositus (family O, III-4) was identified in the pilot study (chapter 5). He had been seen by the neurology service in the advanced stages of a progressive neurologic condition and had died at the age of 31 years. He presented two years prior to this with progressive cerebellar ataxia. In the late stages of this illness he was found to have severe gait and limb ataxia with dysarthria, dementia, hypogonadotropic hypogonadism and diffuse muscle wasting. Reflexes were depressed in the lower limbs and there was a distal sensory neuropathy. His two younger brothers were assessed prospectively.

A brother (III-2) died at the age of 33 years with a similar illness which evolved over an eight year period. Prior to this, he had been documented as having hypothalamic hypogonadism (by the Endocrine service at Groote Schuur Hospital), mild mental retardation and progressive cerebellar ataxia, as well as generalized tonic clonic seizures and peripheral neuropathy. He also had depressed tendon reflexes, amyotrophy and predominantly proximal weakness.

The oldest sibling (family O, III-1), aged 46 years, had a one year history of mild weakness of the legs. He had mild kyphoscoliosis and features of hypogonadism (small genitalia with poorly developed secondary sexual characteristics). The clinical impression was that he had a low intelligence

quotient but he not formally tested. Muscle tone and reflexes were increased in the limbs and there was mild proximal weakness. He was not clinically ataxic, but complained of slight unsteadiness when walking. Optokinetic nystagmus and smooth pursuit eye movements were normal.

Endocrine function tests were undertaken and these revealed low serum testosterone (5.6 nmol/l, normal: 10-35) and normal levels of LH (15 nmol/l, normal: 3-18) and FSH (8.4 nmol/l, normal: 3-15). Both FSH and LH showed a normal but slightly delayed incremental response to stimulation with gonadotropin releasing hormone. This finding is consistent with hypothalamic hypogonadism (ie. the hypogonadism is not due to the inability of the pituitary gland to secrete gonadotrophins but is due to the absence of pituitary stimulation by the hypothalamic releasing hormones). Growth hormone and thyroid function tests were normal.

A mitochondrial encephalopathy was considered as a possible diagnosis in this family in the light of the muscle weakness, history of seizures and multisystem involvement (although hypogonadism is not one of the recognized features of this group of conditions). A muscle biopsy was done but this did not reveal ragged red fibres and there were no morphologic abnormalities of the mitochondria on electron microscopy of the biopsy specimen.

At that time the technology to study the point mutations of mitochondrial DNA had not yet become available locally. MRI scan showed mild cerebellar atrophy.

A younger brother (III-3), complained of gait deterioration with weakness in the limbs and troublesome muscle cramps at night. Clinically there were no features of hypogonadism. He had horizontal nystagmus, loss of smooth pursuit eye movements and reduced optokinetic nystagmus. There was mild (grade 4+/5) proximal weakness and the tendon reflexes in the lower limbs were reduced. He had mild incoordination in the limbs, worse on the left, together with a moderate gait ataxia (ataxia score 17). Higher mental function and sensory examination were normal. He gave a history of having had two generalized seizures prior to the assessment.

The mother of the affected males (II-2) was asymptomatic, but when assessed at the hospital she was found to have mild cerebellar signs in the lower limbs, mild proximal weakness of the hip girdle and absent ankle jerks.

8.5.2 DISCUSSION OF FAMILY O

Affected individuals in this family show a wide variety of clinical signs. Two brothers (III-1, III-3) had hypogonadism and had not reproduced, and a third brother had neurological involvement without hypogonadism. The mother was asymptomatic but had neurological signs. Holmes (1907a) described a familial autosomal recessive progressive cerebellar ataxia associated with hypogonadism, and Harding (1984c) has reviewed subsequent reports of this association. Affected individuals have progressive gait and limb ataxia, usually starting in the third or fourth decade, associated with dysarthria, nystagmus,

titubation and intention tremor (Volpe et al., 1963). Tendon reflexes are normal, hypoactive or even increased (Berciano et al., 1982b). Distal sensory loss (Boitelle et al., 1956) and mental retardation (Lowenthal et al., 1979) were reported in some families. Dementia may develop (Matthews & Rundle, 1964; Berciano et al., 1982). The external genitalia are small, secondary sexual characteristics are poorly developed. These features are evident from the expected time of puberty.

The hypogonadism associated with this disorder is usually hypogonadotropic (low levels of circulating sex hormones and gonadotrophins) (Berciano et al., 1982b). Endocrine evaluation in 4 sporadic cases (De Michele et al., 1993) showed heterogeneity of the hypogonadism with both high and low levels of gonadotrophins in the affected individuals. In contrast to family O above, others (Fok et al., 1989; Bhatia et al., 1993) have described individuals with a similar phenotype who had low gonadotrophin levels which did not rise on stimulation with gonadotrophin-releasing-hormone, indicating a defect in the production or release of gonadotrophins by the pituitary gland.

Although ataxia and hypogonadism usually occur together, Lowenthal et al. (1979) described a family in which a neurologically affected sibling had normal sexual development. This finding parallels that in family O (individual III-3 had ataxia but no hypogonadism). Incomplete expression of a pleiotrophic gene may explain this phenomenon.

A number of other less frequently described clinical features have been reported in certain families. These include deafness (Matthews and Rundle, 1964; Edwards et al., 1976), distal amyotrophy (Neuhauser and Opitz, 1975), choreoathetosis (Altschul and Kotlowski, 1956), pigmentary retinal degeneration (Boucher and Gibberd, 1969; Edwards et al., 1976; Limber et al., 1989; Baroncini et al., 1991), pes cavus (Boucher and Gibberd, 1969; Volpe et al., 1963) and scoliosis (Neuhauser and Opitz, 1975). In a review of reported pedigrees containing individuals with cerebellar ataxia and hypogonadism, Harding (1984c) has noted that the majority are compatible with autosomal recessive inheritance and some with x-linked recessive inheritance. The latter mode of transmission is supported by the fact that the ratio of affected males to females in reported families is about 2 to 1. In addition the consanguinity rate is not as high as would be expected for a rare autosomal recessive disorder.

In family O above, the mode of inheritance is likely to be x-linked recessive as the mother, at the age of 72 years, has subtle but definite neurological signs, and all her male offspring have the disorder. Although affected individuals from different families have several features in common, the presence of additional clinical manifestations, such as deafness or pigmentary retinal degeneration, suggest genetic hetrogeneity (Harding 1984c).

8.6 CEREBELLAR ATAXIA, OPTIC ATROPHY AND DEAFNESS

8.6.1 PHENOTYPE OF FAMILY P

The proposita (family P, II-2,) was assessed at the age of 63 years. Slowly progressive visual deterioration commenced in childhood and she recalled having difficulty seeing in the dark at the age of 8 years; at 18 years she wore very thick spectacles and was completely blind at 45. When she was 35 years old she became aware of impaired balance and hearing loss which were progressive. At the age of 62 she was confined to a wheel-chair. Cognitive function became impaired during the last year of her illness and she became emotionally labile and had lapses in short term memory. Her husband complained that she had experienced visual and auditory hallucinations.

On clinical examination she was blind and had a supranuclear ophthalmoplegia in all directions. Fundoscopy revealed severe bilateral optic atrophy, but no pigmentary retinopathy. She had bilateral partial sensorineural deafness, absent tendon reflexes, muscle weakness (greater distally with wasting of the small muscles of the hands and feet), and a sensorimotor peripheral neuropathy. She was ataxic in the upper limbs and unable to walk because of ataxia and muscle weakness. Psychometric evaluation of her short term memory was inconclusive. She could read brail fluently. She tended to have verbal perseveration with flight of ideas. She died one year later at the age of 64 years.

Her daughter (III-2) was first assessed at the age of 25 years. Her optic discs appeared normal and her visual acuity (formally tested) was normal. Two years later, however, the left optic disc showed pallor and the acuity in the left eye had deteriorated from 6/6 to 6/12. There were also subtle visual field defects in the left eye field on formal perimetry testing. Six years later at the age of 33 years, there had been further deterioration (visual acuity 6/6 on right and 6/24 on left). The right optic disc appeared normal but in the left eye there was optic atrophy without glial tissue or retinopathy. Visual evoked responses were normal on the right and absent on the left. This finding is consistent with unilateral optic nerve pathology. Because of a suspected radiological abnormality in the intraorbital portion of the left optic nerve seen on MRI scan, surgical decompression and exploration of the left optic nerve was undertaken. However, the left optic nerve appeared normal at operation and there was no evidence of an optic nerve meningioma. At the age of 35 years, the left optic disc was unchanged but there was definite optic disc pallor on the right. No other neurological signs have evolved.

A brother (III-1), aged 32 years, was assessed and thought to have mild optic disc pallor. He had worn spectacles since the age of 17 years. He had bilateral pes cavus with surgically corrected hammer toes. Ankle jerks were absent and joint position sense and pinprick sensation were reduced in the toes. Five years later he had mild bilateral optic atrophy with pupillary escape. His visual acuity was normal and the

fields showed mild peripheral constriction. There were no other abnormal neurological signs, but nerve conduction studies showed electrophysiologic evidence of an axonal sensorimotor peripheral neuropathy.
Clinical examination of the sole surviving sibling (II-3) of the proposita was entirely normal.

Post Mortem findings from the proposita:
Macroscopically the hemispheres were symmetrical, without midline shift or significant enlargement of the third or lateral ventricles; the cortical ribbon appeared intact throughout and the basal ganglia normal, although the Substantia nigra was paler than expected; the white matter was unremarkable and the corpus callosum was not obviously thinned. No other focal lesions were evident macroscopically. Horizontal sections of the hindbrain confirmed the impression of a reduction in size especially of the pons and cerebellum. Symmetrical pallor of the substantia nigra was noted and the inferior olives were reduced in size. Histological sections of four muscles showed evidence of neurogenic atrophy which was most pronounced in the right deltoid muscle. Sections of the cerebrum showed no evidence of infection, infarction, haemorrhage, vasculopathy, myelin-pallor or obvious gliosis. Senile plaques and granuolo-vacuolar degeneration were inconspicuous and Lewy bodies were not demonstrated. There was loss of pigmented neurons in the substantia nigra and locus ceruleus. The inferior olives were atrophic. Sections of the cerebellum revealed diffuse slight diminution in the number of Purkinje cells with thinning of the molecular layer

and atrophy of the dentate nucleus. The middle cerebellar peduncles were reduced in size. The cervical cord showed a symmetrical diminution in the number of anterior horn cells with some of the remaining cells appearing degenerate. The white matter of the anterior, lateral and posterior funiculi was not well preserved. The pathologist attributed these findings to a multi-system atrophy.

8.6.2 DISCUSSION OF FAMILY P

The proposita presented with a slowly progressive neurological illness characterized by optic atrophy and blindness, late onset cerebellar ataxia, peripheral neuropathy and sensorineural deafness. In the later stages intellectual deterioration, ophthalmoplegia and chorea evolved. Both her children are in their late thirties and have asymmetrical optic atrophy without cerebellar signs or deafness. In this family the mode of inheritance is likely to be autosomal dominant with variable penetrance.

There are very few descriptions of familial ataxia with severe symptomatic optic atrophy, deafness and peripheral neuropathy. Van Bogaert (1974) described a family with early onset (first decade) cerebellar ataxia associated with optic atrophy and severe visual impairment, deafness and mental retardation. Some affected members did not have optic atrophy or hearing impairment. Similarly, in another family (Hogan & Bauman, 1977), affected siblings had early onset cerebellar ataxia, optic atrophy and signs of pyramidal tract involvement and some also developed deafness and intellectual deterioration.

The mode of inheritance was thought to be autosomal recessive. Iwashita et al. (1970) described two siblings with bilateral optic atrophy, hearing loss and distal muscle wasting. In an earlier report, Rosenberg (1967) described a family in which 3 affected males had early onset optic atrophy, sensorineural deafness and polyneuropathy without ataxia. In this article he discussed the considerable overlap in clinical signs that are seen in the hereditary spinocerebellar ataxias, inherited neuropathies (including Charcot-Marie-Tooth Disease), inherited optic atrophies and Refsum's disease. Similarly, Hoogendijk and DE Jong (1991) reviewed rare variants of the hereditary motor-sensory neuropathies. Although these unusual descriptions of the hereditary neuropathies were associated with sensorineural deafness, optic atrophy, ataxia and other features, none match the phenotype of family P.

Refsum's disease enters into the differential diagnosis. This rare disorder is inherited as an autosomal recessive trait and has its onset in childhood or early adulthood. Affected individuals develop cerebellar ataxia, chronic polyneuropathy and visual impairment. However, these individuals have retinitis pigmentosa coupled with elevated blood phytanic acid levels. Other features of this disorder which may occur include neurogenic deafness, cardiomyopathy, cataracts, pupillary abnormalities, and ichthyotic skin changes. The onset, ocular findings and normal phytanic acid levels in family P are not consistent with this diagnosis. Similarly,

other rare metabolic disorders (GM2 Gangliosidoses, abeta-lipoproteinaemia) were excluded on biochemical testing.

Because of the diffuse involvement of the nervous system in the index case and the presence of bilateral optic atrophy in the offspring, a mitochondrial encephalopathy was also considered in the differential diagnosis. The phenotype of this family was not typical, however, of any of the better characterized subgroups of the mitochondrial cytopathies (viz. Kearns-Sayre syndrome, MERRF, MELAS, Leber's hereditary optic neuropathy). Nevertheless, the clinical spectrum of these disorders is wide and still not fully clarified. A wide range of neurological signs has been described following mutations of the mitochondrial DNA and these include cerebellar ataxia, optic atrophy, dementia, myoclonus, generalized seizures, deafness, spasticity, impairment of position and vibration sense, myopathy, lactic acidosis, stroke-like episodes, external ophthalmoplegia, retinitis pigmentosa, and cardiac conduction defects (Morgan-Hughes, 1986; Bercovic et al., 1989). The mitochondrial encephalopathies have emerged as an important cause of hitherto undiagnosed progressive neurologic syndromes. There is also considerable intrafamilial variation in the clinical presentation of these disorders (Berkovic et al., 1989). This may be due to varying ratios of wild type and mutant mitochondrial DNA present in different oocytes, as well as to different patterns of mitotic segregation of mitochondrial DNA during early embryogenesis (Di Mauro et al., 1985; Rosing et al., 1985).

More recently, molecular techniques for the study of the known

mutations of the mitochondrial DNA (Hammans et al., 1991) have become available locally. Blood and skin biopsy specimens were obtained from an affected member of this family (III-1) and the assays of pyruvate dehydrogenase and pyruvate carboxylase activity were normal. There were no mutations at the mitochondrial DNA base pairs 3242, 3271, and 11778 (this work was undertaken by Dr. E.P. Owen, Department of Chemical Pathology, Medical School, UCT). Further tests for other mitochondrial DNA mutations are to be done in the future.

In conclusion, it must be emphasized that although the autopsy findings from the proposita fall within the spectrum of the spinocerebellar ataxias, the phenotype in this family may well be unique.

8.7 CEREBELLAR ATAXIA, MENTAL RETARDATION, MOTOR NEURONE SYNDROME AND MACULAR DEGENERATION

8.7.1 PHENOTYPE OF FAMILY Q

The index case (III-5) in family Q was referred for assessment by a local institute for the mentally handicapped where he has been living with two younger similarly affected siblings for many years. In his early twenties he developed a gait disturbance which gradually deteriorated and by the age of 39 he was confined to a wheelchair. The clinical assessment at age 45 revealed a mentally retarded man with a maculopathy and peripheral pigmentary retinal changes. Optokinetic nystagmus and smooth pursuit movements were present but reduced. He had a spastic dysarthria, increased tone in the limbs (greater in

the legs) and distal amyotrophy, particularly affecting the small muscles of the hands. Muscle strength was slightly reduced in the upper limbs (4/5 power) but absent (0/5 power) in the legs. All tendon reflexes were brisk except the ankle jerks which were absent. Sensation was difficult to assess because of his mental state. In the upper limbs he had mild cerebellar signs but these could not be evaluated in the legs because of the paraplegia.

A sister (III-8) was similarly affected. Her gait started to deteriorate at the age of 22. At 39 years of age she was assessed and found to be mentally retarded with a spastic paraplegia. She had distal amyotrophy and mild incoordination in the upper limbs. Fasciculations were noted in the thighs. She had a pigmentary maculopathy. Her phenotype was identical to that of the index case.

A younger brother (III-10) started to develop progressive gait ataxia at the age of 15 years. According to the records he was able to walk normally during childhood. By the age of 37 he had spastic paraplegia (grade 3/5 power in the upper limbs, grade 0/5 power in the legs). Both the trapezius and sternocleidomastoid muscles were weak. There was diffuse muscle wasting and fasciculations which were more noticeable in the proximal large muscles. He had wasting of the temporalis muscles and weakness of the facial muscles (obicularis oris and oculi). He had spastic dysarthria with mild dysphagia; the tongue was not wasted or fasciculating. He was mentally retarded and sensation could not be reliably

tested (although it appeared that pinprick sensation was perceived). Optokinetic nystagmus was absent and fundoscopy revealed a maculopathy.

The G1 and G2 gangliosidoses were excluded on specific biochemical testing. Serum lactate level was normal. EMG revealed chronic neurogenic changes (large polyphasic units with decreased recruitment of motor units - see 10.3.2) indicative of lower motor neurone pathology. He died at the age of 38 years from bronchopneumonia.

An affected cousin (III-1) was assessed at the age of 47 years. He had been mentally retarded since childhood and his motor symptoms started at the age of 14 years. By 35 years he was confined to a wheelchair and at the age of 47 years he had a spastic paraplegia with diffuse muscle wasting and fasciculations. There were mild cerebellar signs in the upper limbs.

8.7.2 DISCUSSION OF FAMILY Q

The mode of inheritance in this family is not clear cut, but the fact that 3 affected siblings of unlike sex in one branch of the family had normal parents is suggestive of autosomal recessive inheritance. The occurrence of the disorder in a male cousin whose parents were also unaffected is consistent with this pattern but it would imply that his father, who was not known to be a blood relative of either branch of the family, was heterozygous for the faulty gene. Alternative explanations are autosomal dominant inheritance with non-penetrance, and non-paternity. These issues could not be further elucidated and remained unresolved.

Although affected members of this family had evidence of ataxia in the upper limbs, the spastic paraparesis and diffuse neurogenic atrophy dominated the clinical picture as this disorder progressed. Mental retardation and macular degeneration were the other notable features.

Early descriptions of hereditary spastic paraplegia date back to the late 19th century (Seeligmüller, 1876; Strümpell,1880). The "pure" syndrome (in which the abnormality is virtually confined to a spastic paraparesis) is more common than the complex varieties of the disease (Harding, 1984d). Clearly, family Q does not fall within the scope of "pure" familial spastic paraplegia. Sutherland (1975) and Harding (1984e) have reviewed a variety of very rare and heterogeneous familial disorders with spastic paraplegia and additional neurological features (such as cerebellar ataxia, amyotrophy, mental retardation, retinal degeneration, optic atrophy, extrapyramidal involvement, sensory neuropathy and skin changes). The phenotype in this family is similar to that described by Kjellin (1959,1975) in two pairs of brothers from separate families. In his description, the affected individuals had mental retardation from birth and developed progressive spastic paraparesis around the age of 25 years. This was associated with distal amyotrophy, dysarthria and central retinal degeneration. The pigmentary changes appeared to affect the macula more than the peripheral retina and visual acuity was relatively well preserved. Only a few isolated reports of a similar phenotype have appeared in the literature (Ledic and Van Bogaert, 1960; Gilman and Horenstein, 1964). Ataxia was not a feature in Kjellin's

report. Cross and McKusick (1967) described a recessive form of spastic paraplegia with cerebellar signs and distal amyotrophy. In Kjellin's patients with spastic paraplegia, the distal amyotrophy and fasciculations were noted in the small muscles of the hands, but two affected individuals also had fasciculations and atrophy of the leg muscles. Muscle biopsy from one of these persons showed chronic neurogenic changes. Kjellin's report does not include a description of the phenotype in the advanced or terminal stages of the disorder and it is uncertain whether these individuals ultimately developed more generalized atrophy and fasciculations. Garland and Astley (1950) described a pattern of global atrophy with familial spastic paraplegia.

The combination of upper motor neurone signs and severe generalised muscle wasting with fasciculations in the later stages of the disorder is seen in amyotrophic lateral sclerosis. The mental retardation and maculopathy, however, are not in keeping with those unusual familial amyotrophic lateral sclerosis variants in which some affected persons also have dementia or parkinsonism (Hudson, 1981; Mulder et al., 1986).

It is conceivable that similar cases to those seen in family Q are under-reported in the literature as the retinal changes may be easily overlooked if the macular region is not examined.

8.8 SPASTIC PARAPARESIS WITH ATAXIA AND DYSTONIA

8.8.1 PHENOTYPE OF FAMILY R

In family R, only the proposita (II-2) was living in the Cape Town area and available for assessment. At 28 years she developed a gait disturbance with frequent falls. This progressed very slowly and twelve years later, she was still able to walk independently with a stick. In addition to her deteriorating gait and progressive weakness in her legs, she also complained of urinary frequency and a tendency for her head to move backwards spontaneously, so that she appeared to be looking at the ceiling.

By the age of 56 years she was confined to a wheel chair. At 66 years she was assessed and found to have a spastic paraparesis (5/5 power in the upper limbs and 2/5 power in the legs). All the tendon reflexes were increased and the plantar responses were extensor. Her speech was slightly slurred and there was mild ataxia with an intention tremor in the upper limbs. She had horizontal nystagmus, impaired optokinetic nystagmus, reduced smooth pursuit eye movements, supranuclear ophthalmoplegia, and partial ptosis. There was no retinopathy or optic atrophy. In addition to these clinical signs , she had a focal dystonia with retrotorticollis. Sensation was normal.

A brother (II-5) aged 61 years, who lived in East London, was confined to a wheel chair because of paraparesis. His speech was also severely affected. His symptoms had apparently begun at the age of 25 years. The two remaining siblings were

unaffected. All the members of the third generation (oldest aged 43 years) are asymptomatic, but none have as yet been examined for early signs of this disorder. According to the proposita, her maternal grandfather who died at the age of 79 years, was unable to walk normally from a young age. However, further clinical details concerning his condition were not available.

8.8.2 DISCUSSION OF FAMILY R

Only the index case in this family has been evaluated. The predominant clinical feature in this person was the slowly progressive paraparesis. This was associated with a focal dystonia, mild upper limb ataxia and supranuclear ophthalmoplegia. As discussed in 8.7.2, a variety of associated clinical signs have been reported with familial spastic paraparesis. Ferguson and Critchley (1929), and Mahloudji (1963) have described the unusual association of hereditary spastic paraparesis with supranuclear ophthalmoplegia and extra-pyramidal disorders. Brown (1966, 1975) reviewed the data on four families with spastic-ataxic paraplegia, urinary symptoms, dysarthria, mild mental changes, nystagmus, supranuclear ophthalmoplegia and extra-pyramidal signs (viz. limb rigidity, tremor with Parkinsonian features). Other extra-pyramidal abnormalities (eg. involuntary movements, torticollis, dystonia) have also been reported in association with spastic paraplegia (Dick and Stevenson, 1953; Gilman and Horenstein, 1964).

The full spectrum of the phenotype cannot be characterized in

family R without additional prospective data from other affected members.

8.9 CONCLUSIONS:

In this chapter a group individuals with rare atypical syndromes are described. Although the phenotypes in these families show some similarity to diverse and obscure reports in the literature, there are also significant differences. It remains an open question whether there is considerable heterogeneity or whether this merely reflects a variable expression of the same genetic defect.

SECTION IV

SPECIAL INVESTIGATIONS

Chapter 9 DIAGNOSTIC IMAGING

Chapter 10 NEUROPHYSIOLOGICAL TESTS

CHAPTER 9 DIAGNOSTIC IMAGING

		page
9.1	Introduction	130
9.1.1	Background to diagnostic imaging	130
9.2	Methods	132
9.2.1	Sample	132
9.2.2	Procedure and settings	133
9.2.3	Evaluation and scoring of scans	133
9.3	Results	134
9.3.1	Autosomal dominant ataxia	135
9.3.1.1	Inter-observer reliability	135
9.3.1.2	MRI morphology	137
9.3.1.3	Clinical correlations	144
9.3.2	MRI scan of 4 individuals with distinct phenotypes	145
9.4	Discussion	146

CHAPTER 9

DIAGNOSTIC IMAGING

9.1 INTRODUCTION

In order to complete delineation of the phenotype appropriate diagnostic imaging was undertaken in a group of persons with familial cerebellar ataxia. The CT scan topographic patterns of cerebellar atrophy have been described in the literature (Koller et al., 1981; Huang and Plaitakis, 1984; Ramos et al., 1987; Wittkamper et al., 1993). MRI permits better delineation of the posterior fossa structures than does CT scan. It is therefore ideal for documenting the radiographic changes of spinocerebellar ataxia in which the pathological changes are maximal in the cerebellum, brainstem, and spinal cord. A group of individuals from the South African families were selected to have MRI scans in order to document the radiologic changes and to try to correlate the degree of atrophy with the severity of the ataxia. It was not possible to perform MRI scans on every affected person from these families because of geographic and logistic reasons.

9.1.1 BACKGROUND TO DIAGNOSTIC IMAGING

There is a paucity of reports describing the MRI findings in this group of disorders. In sporadic cases of spinocerebellar ataxia, the differential diagnosis from other diseases, in particular multiple sclerosis, can sometimes be difficult and MRI is very useful in solving this problem. Ormerod at al.

(1987) described the MRI findings in 8 persons with inherited ataxia (5 persons with autosomal dominant late onset ataxia and 3 with autosomal recessive ataxia). The frequency and anatomical distribution of the atrophy of the intracranial structures in this small series of affected persons was in accordance with the pathologic descriptions. In addition to the atrophy of the cerebellum and brainstem structures, these authors observed high intensity signal lesions in the periventricular regions on the scans of 3 of the 5 persons with autosomal dominant cerebellar ataxia. These lesions differed from those seen in patients with multiple sclerosis. The number of persons in each subgroup was too small to permit characterization of MRI changes. In 2 subsequent reports (Nabatame et al.,1988; Bradac et al.,1989) atrophic changes seen on MRI in persons with familial and sporadic ataxia were described but high intensity periventricular lesions were not observed. MRI scanning of 28 persons with sporadic late onset cerebellar ataxia differentiated a group with pure cerebellar atrophy from another group with cerebellar and brainstem atrophy (Klockgether et al.,1993). The scan findings correlated with the clinical assessments as some of these individuals were thought to have a pure cerebellar syndrome and others were thought to have olivopontocerebellar atrophy because of additional non-cerebellar signs. Wüllner et al. (1993) used MRI to study 61 persons with various types of ataxia including 13 individuals with autosomal dominant ataxia (type 1 Harding). In this group the morphologic changes were not uniform, but the authors did not attempt to correlate the

extent and degree of the morphologic changes with the duration and severity of the disorder.

More recently, in certain specialized centres, cerebellar and brainstem morphology can be evaluated quantitatively with an image analyzer and a computerized interpretation programme (Schroth et al.,1990). These measurements require newly developed software which calculates the amount of cerebral tissue within an defined region of interest. A different, steriological method of systematic sampling (Escalona et al., 1991) was devised and used on 37 normal volunteers to determine cerebellar volumes. This particular study demonstrated that gender accounted for significant variability in cerebellar volumes. Although these exciting techniques offer the potential for providing determinations of the volumes of anatomic structures, the standardized values based on data from large numbers of controls of different ages and sex are not widely available for any given method. The technology to calculate cerebellar volumes is not currently available locally and for this reason a qualitative assessment of each scan was undertaken by 3 independent examiners (see 9.2.3).

9.2 METHODS

9.2.1 SAMPLE

27 persons with familial ataxia had MRI scans.
Twenty three (10 males and 13 females) had the same phenotype (viz. Adult onset autosomal dominant ataxia with retained

reflexes) which has been discussed in detail in chapter 7; the remaining 4 individuals had clinically distinct phenotypes.

9.2.2 PROCEDURE AND SETTINGS

The scans were performed using MRI equipment operating at 0.5 Tesla. Supra and infratentorial regions as well as the cervical spinal cord were investigated using spin-echo techniques with proton density, T1 and T2 weighted images in the axial and sagittal planes. The MRI settings are listed in table 9.1.

TABLE 9.1 MRI SETTINGS

Axial T2 and proton density:	TR: 2000ms TE: 30 ms and 90 ms slice width: 6mm slice gap: 3mm field of view: 20cm acquisition matrix: 256 x 256 number of averages: 1
Axial T1 images:	TR: 700 ms TE: 27 ms slice width: 6mm slice gap: 3mm field of view: 20cm acquisition matrix: 256 x 256 number of averages: 2
T1 saggital images	TR: 600 ms TE: 27 ms slice width: 5 mm slice gap: 1 mm field of view: 24 cm acquisition matrix: 256 x 256 number of averages: 2

[TE: time to echo; TR: time to repetition]

9.2.3 EVALUATION AND SCORING OF SCANS

Each scan was evaluated independently by 3 neuroradiologists, all of whom had extensive MRI experience. All 3 examiners were regularly interpreting MRI scans including the assessment of many normal scans. The radiologists were asked to score the

severity of the atrophic changes on each scan in 5 categories (viz.: cerebellar atrophy; brainstem atrophy; spinal cord atrophy; cortical atrophy; as well as a"global score" for the whole scan). A numerical scoring system ranging from 0 (normal) to 9 (severe) was applied to each category. The radiologists were unaware of the severity of the clinical signs.

Inter-observer reliability was assessed by correlating the rating scores of the 3 examiners in each category using the Spearman rank correlation test. An "averaged global score" was derived in order to obtain an optimal qualitative evaluation of the atrophic changes for each scan (ie. summation of global scores by the 3 raters divided by 3). All the averaged global scores for each scan were then correlated with the individual global scores of the 3 examiners in order to verify their use as a reliable radiologic index. Finally, the averaged global scores for each scan were correlated with the individual's clinical scores (of ataxia severity) in order to determine whether the severity of the atrophic changes paralleled the severity of the clinical signs.

9.3 RESULTS

The MRI scans of those individuals who share the same phenotype were analysed separately from the 4 individuals with clinically distinct phenotypes.

9.3.1 AUTOSOMAL DOMINANT ATAXIA:

9.3.1.1 INTER-OBSERVER RELIABILITY

There was good inter-observer reliability for the assessment of the degree of cerebellar atrophy on the MRI scans. The high correlations between the rating scores of the 3 examiners are shown in table 9.2. These were consistent and none of the correlations between the 3 raters were significantly different.

TABLE 9.2 CORRELATION TABLE FOR THE SCORING OF CEREBELLAR ATROPHY

		A	B	C
A	r:	1.0000	0.7739	0.8012
	p:	0.0000	0.0003	0.0002
B	r:		1.0000	0.8126
	p:		0.0000	0.0001
C	r:			1.0000
	p:			0.0000

[A = examiner A, B = examiner B, C = examiner C]

Similarly, there was good inter-observer reliability in the scoring of the degree of atrophy for the brainstem, spinal cord and cerebral cortex (see Tables 9.3 to 9.5). The inter-observer reliability in the scoring of cortical atrophy was not as good as that for the cerebellum, brainstem and spinal cord, but was nevertheless homogeneous in that the correlation coefficients did not differ significantly from one another (see Table 9.5)

TABLE 9.3 CORRELATION TABLE FOR THE SCORING OF BRAINSTEM ATROPHY

		A	B	C
A	r:	1.0000	0.8236	0.8825
	p:	0.0000	0.0001	0.0000
B	r:		1.0000	0.8128
	p:		0.0000	0.0001
C	r:			1.0000
	p:			0.0000

[A= examiner A, B= examiner B, C= examiner C]

TABLE 9.4 CORRELATION TABLE FOR THE SCORING OF SPINAL CORD ATROPHY

		A	B	C
A	r:	1.0000	0.6091	0.6704
	p:	0.0000	0.0052	0.0021
B	r:		1.0000	0.7907
	p:		0.0000	0.0003
C	r:			1.0000
	p:			0.0000

[A= examiner A, B= examiner B, C= examiner C]

TABLE 9.5 CORRELATION TABLE FOR THE SCORING OF CEREBRAL CORTEX ATROPHY

		A	B	C
A	r:	1.0000	0.5858	0.6802
	p:	0.0000	0.0060	0.0014
B	r:		1.0000	0.5042
	p:		0.0000	0.0180
C	r:			1.0000
	p:			0.0000

[A= examiner A, B= examiner B, C= examiner C]

There was a good correlation between the global scores for each scan by the 3 examiners and the averaged global scores

(viz. summation of the global scores of each scan by the 3 raters divided by 3). Table 9.8 shows the correlation between the global score of the 3 examiners as well as the averaged global score. This table verifies the application of an averaged global score as a reliable index of severity for the individual scans.

TABLE 9.6 CORRELATION TABLE OF GLOBAL SCORES AND AVERAGED GLOBAL SCORES

		A	B	C	AVGS
A	r:	1.0000	0.7426	0.8339	0.9042
	p:	0.0000	0.0000	0.0021	0.0000
B	r:		1.0000	0.7302	0.8704
	p:		0.0000	0.0001	0.0000
C	r:			1.0000	0.9058
	p:			0.0000	0.0000
AVGS	r:				1.0000
	p:				0.0000

[A= examiner A, B= examiner B, C= examiner C, AVGS= averaged global score]

9.3.1.2 MRI MORPHOLOGY:

The MRI scans of the 23 individuals with autosomal dominant late onset cerebellar ataxia revealed variable degrees of atrophy of the cerebellum, brainstem, spinal cord and cerebral cortex. In the cerebellum the atrophic changes were diffuse and not confined to the upper vermis or anterior part of the cerebellum. No high intensity signals were observed on any of the scans. The variation in the degree of the atrophic changes in the cerebellum, brainstem, spinal cord and cerebral cortex observed in each of the 23 scans (average scores) is shown in table 9.7. The global average scores of the 23 scans

revealed that 2 were graded as normal, 11 were graded as mild, 4 had moderate atrophic changes, 5 were moderately severe and 1 had severe atrophic changes. Figure 9.1 is an example of a normal MRI scan and figures 9.2, 9.3, 9.4, and 9.5, illustrate examples of the mild, moderate and severe atrophic changes. All three examiners were in complete agreement with the grading of the severity of the morphologic changes observed in these three examples.

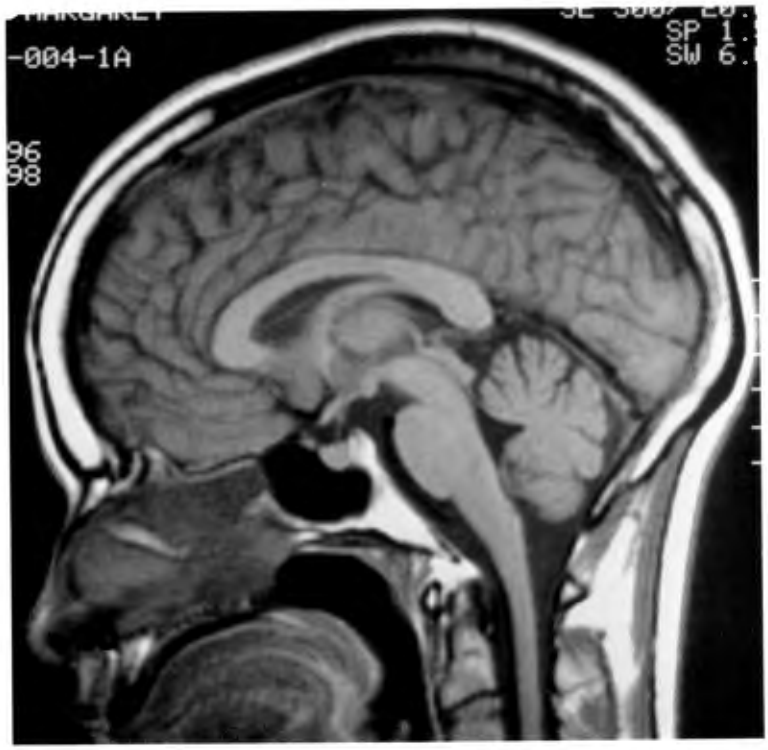
TABLE 9.7 MRI MORPHOLOGY OF LATE ONSET DOMINANT ATAXIA

	Cerebellar atrophy	Brainstem atrophy	Spinal cord atrophy	cortical atrophy
scan 1	++	+++	++	++
scan 2	+++	++	++	++
scan 3	++	++	++	+
scan 4	++	+	+	N
scan 5	+	+	+	N
scan 6	+	N	N	N
scan 7	++	+++	++	+
scan 8	++	++	+++	++
scan 9	++	++	++	+
scan 10	+	+	+	N
scan 11	++	++	+	+
scan 12	+	+	+	+
scan 13	+	+	+	N
scan 14	N	N	N	N
scan 15	++	+	+	N
scan 16	+	+	+	N
scan 17	+	+	+	+
scan 18	+	+	+	N
scan 19	+	+	+	N
scan 20	N	N	N	N
scan 21	+	+	N	N
scan 22	++	++	+	N
scan 23	+	+	+	+

[+ = mild, ++ = moderate, +++ = severe, N = normal]

FIGURE 9.1 (a, b) NORMAL MRI SCAN

a) Midline sagittal T1 weighted image



b) Axial T1 weighted image through the posterior fossa.

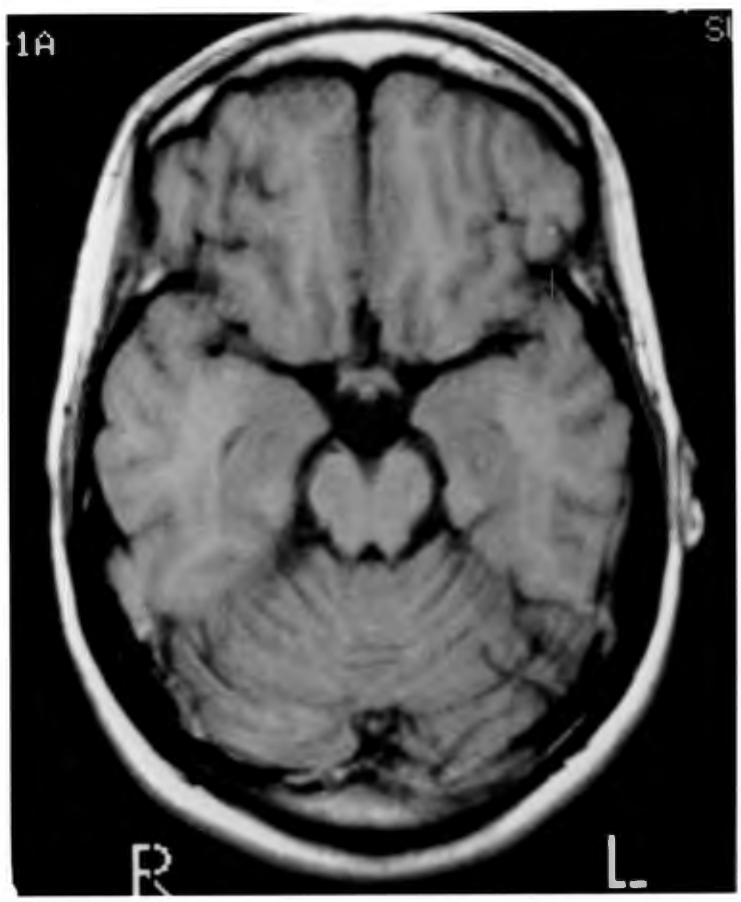


FIGURE 9.2 (a, b) MILD ATROPHY OF THE CEREBELLUM AND BRAINSTEM

a) Midline sagittal T1 weighted image

b) Axial T1 weighted image through the posterior fossa.

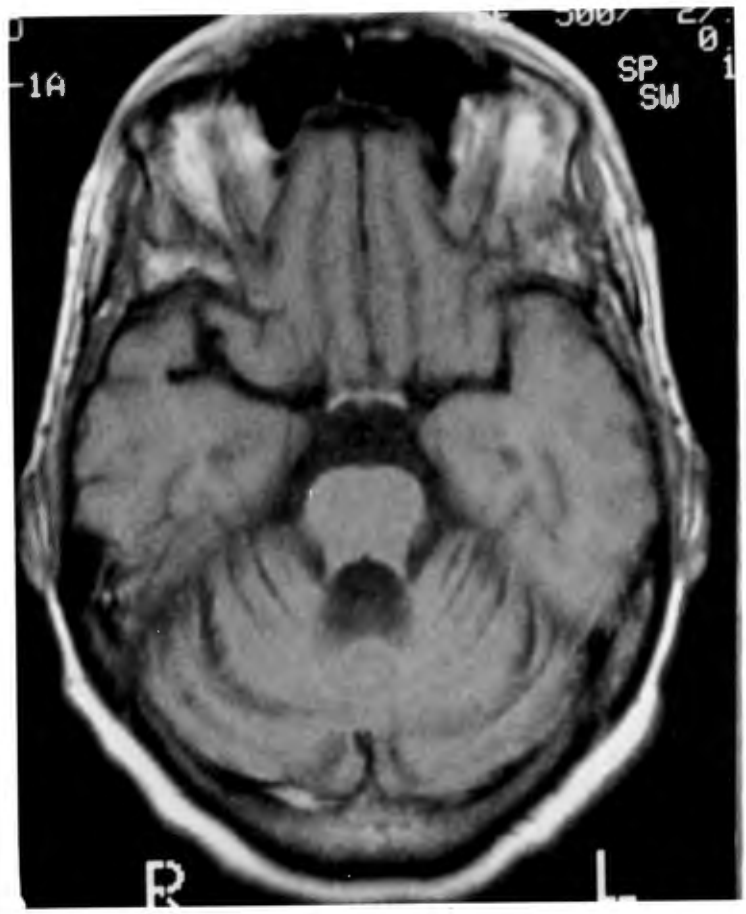
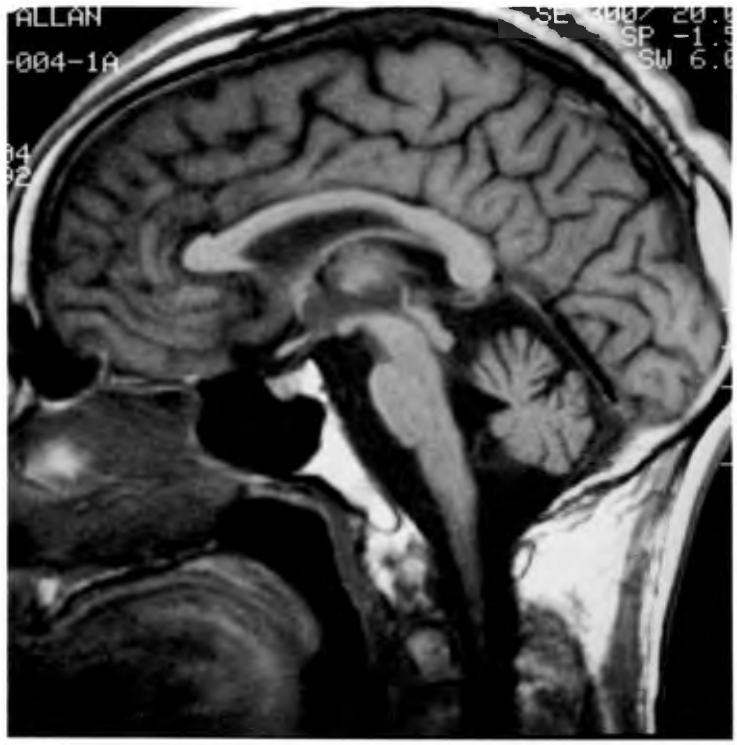


FIGURE 9.3 (a, b) MODERATE ATROPHY OF THE CEREBELLUM AND BRAINSTEM

a) Midline sagittal T1 weighted image



b) Axial T1 weighted image through the posterior fossa.

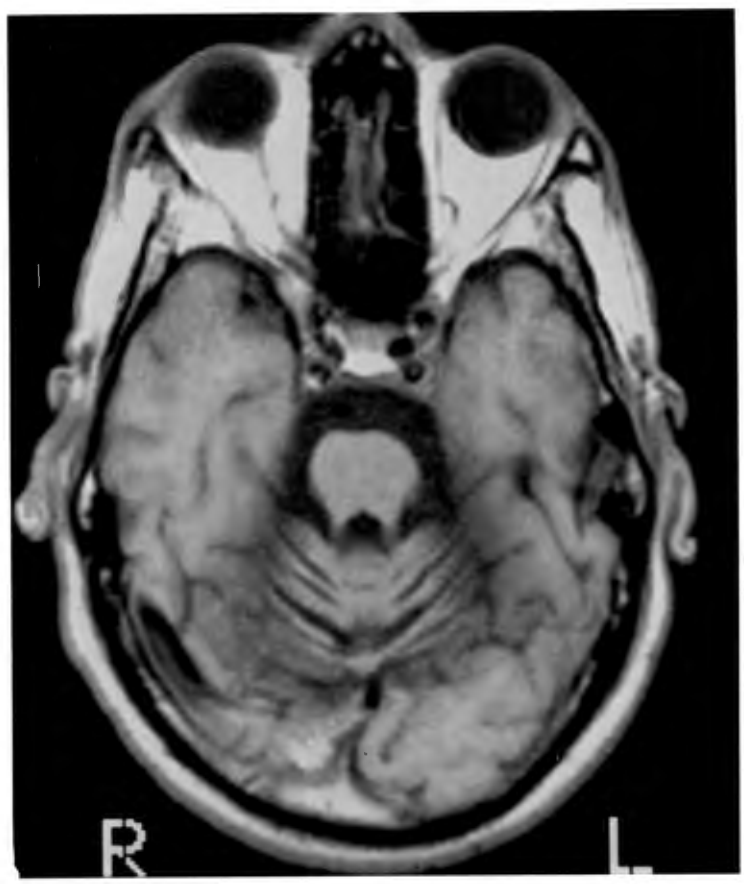
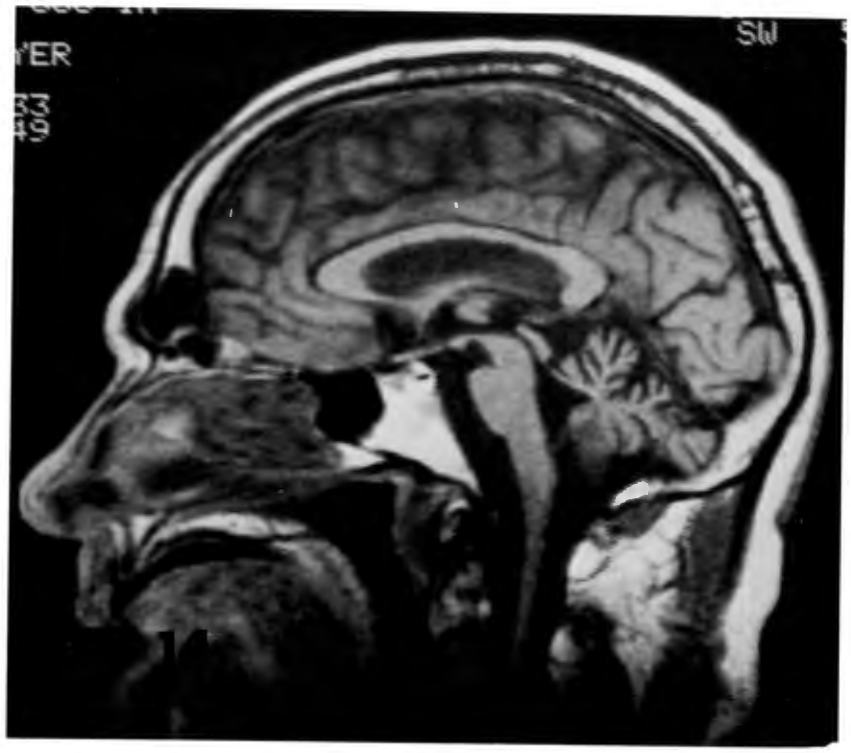


FIGURE 9.4 (a, b) SEVERE ATROPHY OF THE CEREBELLUM AND BRAINSTEM

a) Midline sagittal T1 weighted image



b) Axial T1 weighted image through the posterior fossa.

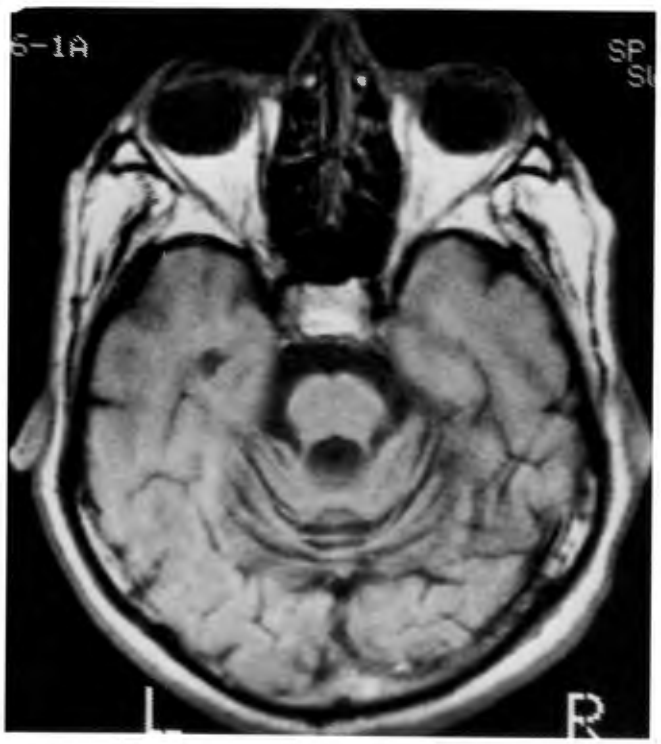
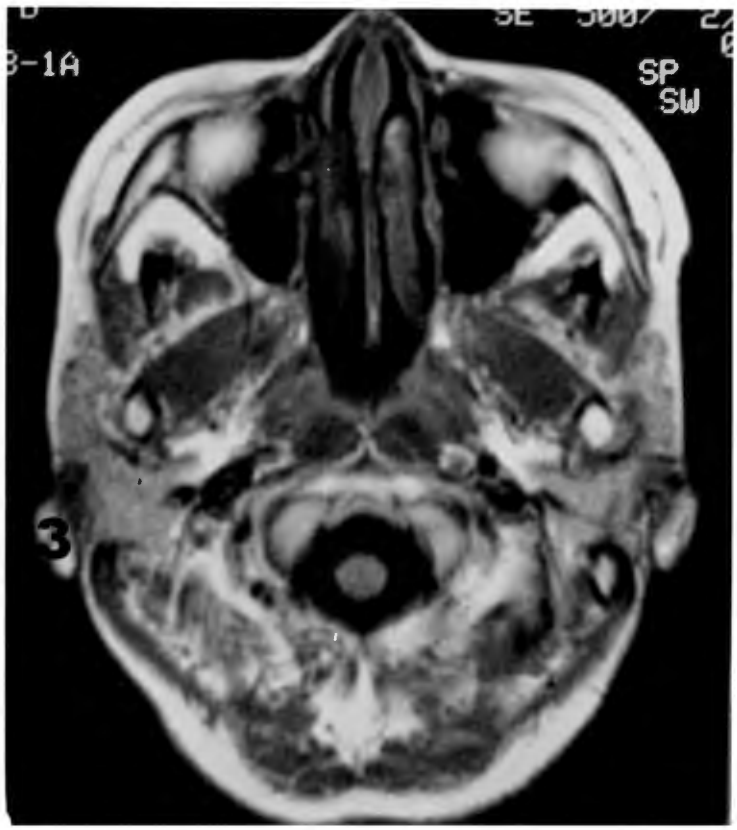


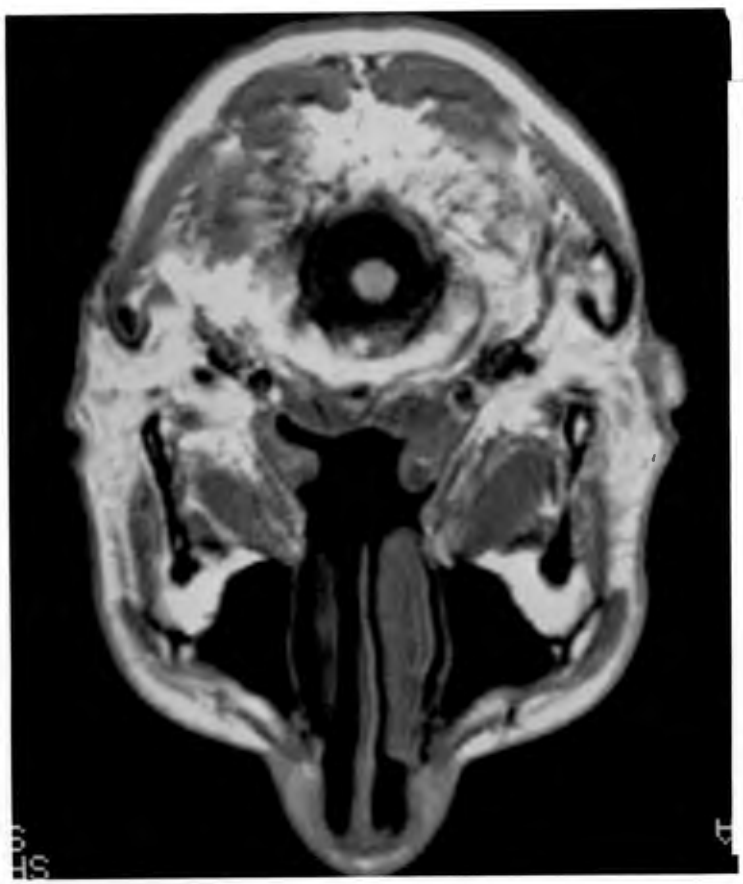
FIGURE 9.5 MILD (a), MODERATE (b), AND SEVERE (c) ATROPHY OF THE SPINAL CORD

Axial T1 weighted images through the proximal cervical cord

a)



b)



c)

9.3.1.3 CLINICAL CORRELATIONS:

The grade of ataxia severity of each affected person was correlated with the grade of the atrophic changes on the MRI scan (averaged global scores). This revealed a moderate correlation between the clinical and radiographic scores ($p > .514$ and $r < 0.0121$ Spearman rank correlation coefficient). Table 9.8 demonstrates the clinical and corresponding radiographic grades of severity. In 16 of the 23 individuals the severity of the ataxia was graded in a higher category (ie more severe) than the severity of the atrophic changes on MRI scan. In 2 individuals the degree of atrophy on the scans was greater than the clinical score for ataxia and 5 persons had the same grade for ataxia and atrophy. Two individuals with normal scans had definite mild ataxia. This data indicates that in most individuals with this phenotype the clinical signs are more severe and tend to precede the morphologic changes seen on the MRI scan.

TABLE 9.8 COMPARISON OF CLINICAL AND RADIOGRAPHIC INDICES

	Severity of Ataxia (ataxia score)	Severity of Atrophy on MRI (ave global score)
scan 1	severe	moderately-severe
scan 2	moderate	severe
scan 3	severe	moderately-severe
scan 4	severe	moderate
scan 5	mild	mild
scan 6	mild	mild
scan 7	moderate	moderately-severe
scan 8	severe	moderately-severe
scan 9	severe	moderately-severe
scan 10	moderately-severe	mild
scan 11	severe	moderate
scan 12	severe	mild
scan 13	moderate	mild
scan 14	mild	normal
scan 15	severe	moderate
scan 16	mild	mild
scan 17	mild	mild
scan 18	moderate	mild
scan 19	moderate	mild
scan 20	moderate	normal
scan 21	moderate	mild
scan 22	moderate	moderate
scan 23	moderately-severe	mild

9.3.2 MRI SCAN OF 4 INDIVIDUALS WITH DISTINCT PHENOTYPES

The eldest sibling in family O (see chapter 8.5) presented with hypogonadism, mild kyphoscoliosis and mild cerebellar signs. MRI scan revealed mild atrophy of the cerebellum, brainstem, and cerebral cortex while the spinal cord was considered to be normal.

The illness of the proposita of family P was characterised by optic atrophy with blindness, sensorineural deafness, cerebellar ataxia, sensorimotor peripheral neuropathy and dementia. Her MRI scan revealed moderate generalized atrophy of the cerebral cortex, brainstem, spinal cord and cerebellum. The MRI scan of the index case in family M showed similar

generalized moderate atrophy involving cerebellum, brainstem, and spinal cord, with mild cortical atrophy. The phenotype was characterised by late onset visual failure due to macular degeneration, along with cerebellar ataxia.

The youngest affected sibling in family Q was found to be mentally retarded at an early age and developed progressive ataxia followed by spastic paraplegia. Ultimately diffuse muscle wasting and fasciculations developed (see chapter 8.7). The MRI scan showed mild cerebellar, brainstem and spinal cord atrophy with severe cortical atrophy.

9.4 DISCUSSION

In the group of patients with autosomal dominant cerebellar ataxia MRI scan demonstrated the morphological changes which affect the cerebellum, brainstem, spinal cord and cerebral cortex to varying degrees. These findings were in accordance with the gross neuropathological changes described in this group of disorders (see chapter 1.6; Koeppen and Barron,1984). No focal high intensity lesions were observed in this subgroup. There was a moderate correlation between the severity of the atrophic changes and the clinical ataxia syndrome. In the majority of affected persons the clinical scores for ataxia were greater than the scores allocated to their corresponding MRI scans. This finding is not unexpected and a number of factors could account for these discrepancies. Although five categories of severity (ie. normal, mild, moderate, moderately severe, severe) were defined for the

scoring of both the morphology of the MRI scans and the clinical severity of ataxia, both were essentially qualitative measurements. The presence of pyramidal tract signs, sensory abnormalities and dementia would not be reflected in the clinical score, which only attempted to quantify the severity of cerebellar ataxia. Conversely, the morphologic changes observed on the scans reflect a wider disease process. Although there was good correlation between the scores allocated to the scans by the three different examiners, volumetric assessments are likely to provide a more accurate evaluation of the atrophic changes once this technology becomes more widely available. Early in the course of the disorder it is likely that the clinical signs reflect the underlying biochemical abnormalities and that this precedes any radiologically evident changes.

In our hands MRI scans were not helpful in confirming the diagnosis in instances where the clinical signs were equivocal or mild. Two individuals with early signs of the disorder (mild ataxia) had MRI scans which were rated as normal. In Huntington disease, patients may also have normal CT scans in the early stages (Hayden et al., 1986). In my experience, when the scans demonstrated equivocal abnormalities, there was usually little doubt of the clinical diagnosis. The MRI scan was unhelpful as an early or presymptomatic indicator of the disorder, but proved to be particularly useful in the evaluation of persons with sporadic late onset cerebellar ataxia by excluding other potential causes for the clinical manifestations.

MRI scans of the 4 individuals with unique phenotypes demonstrated atrophic changes in the central nervous system. These were non-specific and of no help in distinguishing individual syndromes.

CHAPTER 10 ELECTROPHYSIOLOGICAL STUDY

		page
10.1	Introduction	150
10.2	Methods	151
10.2.1	Sample	151
10.2.2	Technique	152
10.3	Results	154
10.3.1	Nerve conduction studies in persons with the same phenotype	154
10.3.2	Nerve conduction studies in persons with distinct phenotypes	155
10.4	Discussion	156

CHAPTER 10

ELECTROPHYSIOLOGICAL STUDY

10.1 INTRODUCTION

A few reports have described peripheral neuropathy in individuals with dominantly inherited ataxia. Nerve conduction studies have been performed in a small number of individuals and the results have been inconsistent (McLeod and Evans, 1981). Some reports have described reduced or absent sensory action potentials in individuals with dominant ataxia and reduced tendon reflexes (Wadia, 1980). Although sensory neuropathy may be a feature of ADCA, sensory nerve conduction may be normal in the presence of clinical sensory loss (Harding, 1982). She suggests (1984) that the clinical, pathological and electrophysiological data favour a dying-back axonopathy, which selectively effects centrally directed nerve fibres in the posterior columns before the peripherally directed ones, to account for sensory abnormalities and the loss of tendon reflexes. Loss of anterior horn and dorsal root ganglia cells at autopsy has been reported in some individuals with OPCA and distal amyotrophy (Sigwald et al.,1964; Taniguchi and Konigsmark, 1971; Woods and Schaumberg, 1972; McLeod and Evans, 1981). Evidence favours the primary pathological lesion to be in the anterior horn cell rather than the peripheral nerves (Woods and Schaumberg,

1972) although extensive pathological studies of motor nerves have not been done.

10.2 METHODS

For logistic reasons it was not feasible to undertake electrophysiological studies on all the affected persons in the studies. A group of individuals representing the spectrum of familial ataxia in the Western Cape were selected for electrophysiologic studies.

10.2.1 SAMPLE

A total of 22 affected individuals were studied. Seventeen of these persons from 7 different families had the same phenotype (ie adult onset dominant ataxia with retained reflexes; chapter 7). The remaining 5 persons were from 3 families with differing phenotypes (family P: 1 person; family M: 1 person; family Q: 3 persons). In the group of individuals with the same phenotype there were 9 males and 8 females with a mean age of 38.5 years (range = 18 - 57 years). The severity of the ataxia within this group is illustrated in table 10.1.

TABLE 10.1 SEVERITY OF ATAXIA IN THE SAMPLE

Severity of ataxia	Number of persons
Mild	5
Moderate	5
Moderately severe	3
Severe	4
Total	17

10.2.2 TECHNIQUE

All the nerve conduction studies were performed according to Groote Schuur Hospital neurophysiology laboratory protocol on the Medelec Mystro MS25 machine (figure 10.1). The common peroneal motor and posterior tibial motor responses and the sural sensory (or medial plantar sensory) response were done on all persons in the sample. Electrophysiologic nerve conduction responses were measured with supra-threshold stimuli. Maximum motor amplitudes were measured from baseline to the negative peak of the compound motor action potential and sensory amplitudes were measured from peak to peak after 8 responses were averaged. The sensory latency was measured from stimulus onset to the negative peak of the sensory action potential. Electromyography (EMG) with a standard concentric needle electrode was undertaken in those persons with distal amyotrophy. Skin surface temperature was measured 5 cm above the lateral malleolus and the limb was heated (in a warm water bath at 40 C for 10 minutes if the surface temperature was below 28.5 C). Protocols for nerve conduction studies have been standardized in the Groote Schuur Hospital laboratory and the normal values for the relevant nerves are listed in table 10.2. Consent was obtained from all participating persons by the author.

TABLE 10.2 NERVE CONDUCTION STUDIES : NORMAL VALUES (GSH LABORATORY)

Nerve	Distal latency	Amplitude	Conduction velocity
motor:			
Peroneal	3.1 - 5.9 msec	> 2.0 mV	> 41 m/sec
Tibial	3.0 - 6.0 msec	> 4.0 mV	> 41 m/sec
sensory:			
Sural	3.2 - 4.4 msec	> 6.0 μV	

[msec = milliseconds; mV = millivolts; μV = microvolts; m/sec = metres per second]

FIGURE 10.1 NERVE CONDUCTION STUDIES (GSH, EMG LABORATORY)

An affected person (family G) who participated in the electrophysiological study.

10.3 RESULTS

10.3.1 NERVE CONDUCTION STUDIES IN PERSONS WITH THE SAME PHENOTYPE

Of the 17 persons with the same phenotype only 4 persons had abnormal results on electrophysiologic testing. The nerve conduction velocities in both the posterior tibial motor nerves and common peroneal motor nerves were reduced to values ranging from 33.6 to 37.3 m/s. The distal latencies were normal in all 4 persons and the amplitude of the compound muscle action potential was reduced in only 1 of the 4 persons. The sural sensory response was absent in 1 person and normal in the remaining 3. Needle electromyography was done on 2 of the 4 persons and this confirmed the presence of mild denervation with reinervation in the distal leg muscles. All four individuals with abnormal nerve conduction studies had a moderately severe or severe ataxia score. The results are illustrated in table 10.3. Only the results of the 4 individuals with abnormal tests are reflected.

TABLE 10.3 NERVE CONDUCTION STUDY RESULTS

Person No	Age (yrs)	Severity of ataxia	Peroneal CV (m/sec)	Tibial CV (m/sec)	CMAP ampl.	Sural resp.
1	57	MS	33.7	37.3	N	A
2	36	MS	34.8	36.2	N	N
3	34	S	34.7	33.6	N	N
4	36	S	35.5	36.2	R	N

[CV= conduction velocity; CMAP= compound motor action potential; No = number; yrs = years; ampl = amplitude; resp = response; m/sec = metres per second; MS = moderately severe; S = severe; N = normal; A = absent; R = reduced]

10.3.2 NERVE CONDUCTION STUDIES IN PERSONS WITH DISTINCT PHENOTYPES

The proposita from family P who developed optic atrophy, deafness and cerebellar ataxia (chapter 8.6.1) had an EMG which confirmed the presence of a distal axonal sensorimotor polyneuropathy. The CMAP's of the peroneal and tibial motor nerves were reduced (1.0 mv and 0.2 mv respectively) and the conduction velocities were also mildly reduced (40.9 ms and 39.2 ms respectively). The sural sensory response was also reduced (amplitude 3.0 microvolts). The distal latencies in the peroneal, tibial, and sural nerves were all normal. Consent for needle EMG examination was refused.

Electrophysiologic studies in the proposita of family M, aged 48 years, with macular degeneration and cerebellar ataxia (chapter 8.3.1) did not reveal any evidence of a polyneuropathy. The common peroneal motor, sural sensory, median ulnar and sensory responses were all normal.

The 3 affected persons from family Q, age 37, 42, and 50 (with cerebellar ataxia, motor neurone syndrome, mental retardation and macular degeneration; see chapter 8.7.1), had extensive EMG studies in both upper and lower limbs. In the lower limbs the motor responses were absent or markedly reduced in amplitude and the sural sensory response was either absent (2 persons) or reduced in amplitude (1 person). The motor responses in the upper limbs revealed reduced CMAP amplitudes with mildly reduced or normal conduction velocities in all 3 persons. The median and ulnar digital sensory responses were

reduced in 2 of the 3 persons. Needle EMG of several proximal and distal muscles (eg tibialis anterior, gastrocnemius, abductor hallucis, quadriceps femoris, gluteus medius, deltoids, abductor digiti minimi, first dorsal interosseous muscles) revealed electrophysiologic evidence of extensive denervation with reinervation (ie increased insertional activity with frequent complex repetitive discharges, 1 to 3+ fibrillation potentials, large polyphasic motor unit potentials and reduced recruitment of motor units).

10.4 DISCUSSION

Four individuals with autosomal dominant ataxia had evidence of a mild motor polyneuropathy with reduced motor conduction velocities in at least 2 peripheral nerves. Although all had moderately severe or severe ataxia scores, motor signs were not clinically prominent. All 4 persons were subsequently shown to have the same genotype. This is clearly a late finding in this phenotype and is not valuable clinically in differentiating between those individuals with the same phenotype but a different genotype (2 other individuals, with a moderately-severe and a severe ataxia score respectively, had normal nerve conduction studies and were subsequently shown to have the same genotype as the 4 persons with neuropathy). These findings indicate that a motor or sensori-motor neuropathy is a variable and often late manifestation of this phenotype. Nousiainen et al. (1988) found electrophysiological evidence of lower motor neurone involvement, which did not seem to correlate with the duration

or severity of the disease, in a small sample of 10 patients with late onset ataxia. The mean duration of disease in this small sample was, however, 10.7 years (9 of the 10 patients had a duration of disease of 7 years or more).

With regard to those individuals with different phenotypes, the electrophysiologic studies confirmed the presence of a sensorimotor axonal polyneuropathy in the proposita of family P which was evident clinically. Similarly, the affected persons in family Q, all of whom had extensive muscle wasting and fasciculations, were shown to have evidence of widespread chronic active denervation with reinervation in keeping with anterior horn cell disease. Sensory neurones were also affected but not to the same extend as the motor system.

SECTION V

LINKAGE STUDY

Chapter 11 LINKAGE ANALYSIS IN AFFECTED FAMILIES

CHAPTER 11 LINKAGE ANALYSIS IN AFFECTED FAMILIES

page

11.1 Introduction 160

11.2 Methods 161

11.2.1 Linkage analysis with HLA, red blood cell and serum protein markers 161

11.2.2 Microsatellite DNA markers 163

11.2.3 Trinucleotide (CAG) expansion at SCA1 166

11.2.3.1 Statistical analysis 167

11.3 Results 167

11.3.1 Linkage analysis with HLA, red cell and serum protein markers 167

11.3.1.1 Haplotypes and results of linkage analysis in family A 167

11.3.1.2 Results of linkage analysis with HLA in families B, C, D, E, and F 172

11.3.2 Linkage analysis with microsatellite markers 174

11.3.3 Trinucleotide expansion at SCA1 176

11.4 Discussion 182

11.4.1 HLA analysis 182

11.4.2 Linkage analysis with microsatellite markers 183

11.4.3 Trinucleotide expansion at SCA1 187

11.5 Conclusion 188

CHAPTER 11

LINKAGE ANALYSIS IN AFFECTED FAMILIES

11.1 INTRODUCTION

In a few previously published families with autosomal dominant cerebellar ataxia the gene has been assigned to chromosome 6p (SCA1 locus) on the basis of the demonstration of linkage of the disorder to the HLA gene cluster (Yakura et al., 1974; Jackson et al., 1977; Lamm et al., 1985; Rich et al., 1987; Zoghbi et al., 1988,1989; Frontali et al., 1991; Wilkie et al., 1991).

The South African families in the present study were evaluated at different stages of the clinical survey and the chronological sequence of the linkage investigations, initiated at different times during the course of the study, followed developments in the field. Initial linkage studies were an attempt at broad localization of the disorder using several conventional polymorphisms. With the recognition of linkage to the HLA cluster in family A, this locus alone was tested in subsequent families. Once microsatellite DNA markers were available in this region, they were used in preference to earlier markers.

Linkage studies in the largest family (family A) involved the HLA locus (Bryer et al., 1992), serum proteins, red blood cell antigens and enzymes (see 11.2.1). Five other families

(families: B, C, D, E, F), subsequently identified as having the same phenotype as family A were studied for linkage to HLA. The description of closely linked highly polymorphic PCR-based markers led to the analysis of the 5 largest families (families: A, B, C, D, E) using microsatellite markers on chromosome 6 (see 11.2.2).

More recently, the discovery of an expanded trinucleotide repeat at the SCA1 locus (Orr et al., 1993) facilitated the investigation of 11 South African kindreds for this mutation (see 11.2.3).

The methodology and results of the linkage analyses undertaken in the South African ataxia families are discussed in detail.

11.2 METHODS

11.2.1 LINKAGE ANALYSIS WITH HLA, RED BLOOD CELL AND SERUM PROTEIN MARKERS

A large five generation kindred of mixed ancestry with an autosomal dominant form of the disorder (family A) was analysed for linkage to 13 genetic markers (Bryer et al., 1992). Forty four persons of the affected family, spanning three generations, were examined for evidence of the disease and were regarded as being affected if there were clinical signs of gait or limb ataxia. The pedigree of this family is shown in the Appendix. The disorder was inherited as an autosomal dominant trait, no generations were skipped and an equal number of males and females were affected. The age at onset varied from 16-48 years with a mean of 33 years. The

phenotype has been discussed in detail in chapter 8. In view of the late onset, individuals under the age of 16 were excluded from the linkage analysis.

The family was investigated for genetic polymorphisms; the red cell antigens: ABO, Rhesus (RH), Kell (KEL), MNS and Duffy (FY) were detected using standard serological methods (Dunsford et al., 1967). The red cell enzymes: acid phosphatase (ACP1), adenosine deaminase (ADA), adenylate kinase (AK), esterase-D (ESD), 6-phosphogluconate dehydrogenase (PGD), phosphoglucomutase-1 and -2 (PGM1 and PGM2), carbonic anhydrase II (CA2), glyoxalase 1 (GLO1) and the serum proteins haptoglobin (HP), transferrin (TF) and properdin factor B (BF) were determined using standard electrophorectic techniques (Alpers et al., 1972, Harris et al., 1976). HLA-A, B and C typing was done using the standard microlymphocytotoxicity technique (Terasaki et al., 1974). Five other families (families: B, C, D, E, F) with the same phenotype were found to be suitable for a similar analysis, using HLA markers only. HLA haplotypes were assigned to various members of these families using the same standard microlymphocytotoxicity techniques as above (family A).

Ancestral individuals who were required for the linkage analysis but who were not available for examination were classified as "affected" or "not affected" on medical records or histories obtained from surviving relatives.
A total of 195 individuals were at risk of developing the disorder in these 6 families. A person was considered to be

at risk if one parent was affected and the individual was less than 40 years of age.

The method of analysis for HLA haplotypes recommended by Ott (1978) was utilised. The program LIPED was used to compute lod scores with a modification for age-dependent penetrance (Ott, 1974).

11.2.2 MICROSATELLITE DNA MARKERS

Prior to the availability of the microsatellite DNA markers, several RFLP markers were used on the two large South African families with late onset autosomal dominant ataxia (family A and family B). These markers were uninformative, however, and were superceded by the more highly polymorphic PCR-based microsatellite markers. In order to determine the localization of the SCA1 gene on chromosome 6p more precisely, two highly polymorphic microsatellite DNA markers were investigated for linkage with the disease locus.

Five of the largest South African families (families:A, B, C, D, E) were investigated for linkage with the highly informative dinucleotide repeat markers at the D6S89 (Litt, 1990), and D6S260 (Weissenbach et al., 1992) loci distal to the HLA region on the short arm of chromosome 6. These PCR-based polymorphisms were shown to be more closely linked to the SCA1 locus than HLA and are considered to be more definitive markers for the localization of the disorder. All five families had a similar phenotype as described previously in chapter 8. Allele frequencies for each marker were

established by screening a background mixed ancestry population of 50 unrelated individuals.

One hundred and seventeen members spanning three generations were examined for signs of gait and limb ataxia and the pedigree of each family is shown in the appendix. In these kindreds the disease was inherited as a classical autosomal dominant trait, with no generations being skipped and equal numbers of males and females being affected. All 5 families were from the Western Cape geographical region of South Africa and it is possible that they shared a common ancestry. Genomic DNA was isolated from heparinized blood samples taken from affected and unaffected family members. Analysis of dinucleotide repeat length-polymorphisms at the D6S89 and D6S260 loci was performed on 46 individuals from family A, 18 individuals from family B, 8 individuals from family C, 7 individuals from family D and 9 individuals from family E.

PCR was carried out in a volume of 10ul with 200ng of genomic DNA, 10pmol of each primer, 1.5mM $MgCl_2$, 250uM dNTPs, 50mM KCl, 10mM Tris-HCl pH 8.3 and 1.0 unit Thermus aquaticus (Taq) DNA polymerase (BRL). Alpha-dCT^{32}P was added to each reaction at 1uCi. The samples were overlaid with liquid paraffin and an initial denaturation at 94^{0}C for 3 minutes was performed. PCR was carried out with each of the microsatellite markers subjected to 30 cycles using conditions indicated in table 11.1 and a final step of 7 minutes at 72°C to stop the reaction.

TABLE 11.1 PCR CONDITIONS FOR MICROSATELLITE MARKERS

MARKER	DENATURATION		ANNEALING		EXTENSION	
	temp	durn	temp	durn	temp	durn
D6S89	93°C	1min	55°C	1min	72°C	1min
D6S260	94°C	1min	50°C	1min	72°C	1min

[durn = duration]

After completion of the PCR reaction, 2,5ul of each reaction was mixed with 2,5ul of formamide loading buffer, denatured for 5 min at 95^0C and fractionated by electrophoresis on a 6% acrylamide 7.65M urea sequencing gel for 3.0h at 60 watts. Gels were dried and exposed to Agfa Curix film for 20 hours at -70°C.

The computer program LINKAGE, Version 5.03 [13], was used to calculate lod scores between the spinocerebellar ataxia locus and the marker loci D6S89, and D6S260. For the purpose of linkage analysis, all unaffected persons under the age of 40 years were classified as phenotype unknown. Allele frequencies for the microsatellite markers in the linkage analyses were calculated by using 42 independent chromosomes from unrelated individuals from the mixed ancestry population group. Linkage analysis with each of the microsatellite markers was simplified in the families by redefining the observed multiple alleles to a five allele system as described by Ranum et al. (1991).

11.2.3 TRINUCLEOTIDE (CAG) EXPANSION AT SCA1

Blood was obtained from both affected and unaffected individuals from 11 South African families and screened by PCR analysis for the presence of the expanded CAG repeat at the SCA1 locus. In 8 of these families (families: A, B, C, D, E, F, G, J) the phenotype was similar (autosomal dominant cerebellar ataxia type 1, Harding); the clinical details have been discussed in detail in chapter 8. The remaining 3 families (families: K, N, R) had clinically distinct phenotypes which were discussed in chapter 9 (9.1, 9.4, 9.8)

Genomic DNA was isolated directly from venous blood (Bell, Karam and Rutter, 1981). PCR reactions were performed using the Rep1 (5'AACTGGAAATGTGGACGTA 3') and Rep2 (5'CAACATGGGCAGTCTGAG 3') primers (Orr et al., 1993). 250ng of genomic DNA was mixed with 25 pmol of each primer in a total volume of 25ul containing 1.25 mM $MgCl_2$, 250uM dNTPs, 50mM KCl, 1.25% formamide, 10mM Tris-HCl pH 8.3 and 1.0 unit Taq polymerase. Alpha $dCT^{32}P$ was added to the reaction at 2uCi. Reaction samples were initially denatured at 94°C for 3 min, followed by 30 cycles of denaturation (94°C, 30 sec), annealing (55°C, 1 min), extension (72°C, 1 min), and ending with one last cycle of 7 minutes at 72°C. 3 ul of each PCR reaction was mixed with 2 ul formamide loading buffer, denatured at 95°C for 5 min, and electrophoresed through a 6% polyacrylamide/7.65 M urea DNA sequencing gel. Allele sizes were determined by comparing migration relative to a M13 sequencing ladder.

11.2.3.1 STATISTICAL ANALYSIS

To determine the statistical relation between the size of the expanded CAG repeat and the age of onset and duration of the disease, a regression analysis was performed. Linear, logarithmic, and square root transformed data were used for this analysis. Square root and logarithmic transformation of the data for age of onset did not improve the correlation coefficient.

Duration of disease is an index of disease severity; severe disease is characterized by a more rapid clinical course with a shorter interval from onset to a state of dependency or death. As the number of individuals who had died in these families was too small for a meaningful analysis, the time taken to reach a state of dependency (or to acquire a moderately-severe or a severe clinical ataxia score) was used as the index of duration. The relationship between duration of disease and the CAG repeat length was subjected to linear regression analysis.

11.3 RESULTS

11.3.1 LINKAGE ANALYSIS WITH HLA, RED BLOOD CELL AND SERUM PROTEIN MARKERS

11.3.1.1 HAPLOTYPES AND RESULTS OF LINKAGE ANALYSIS IN FAMILY A

The pedigree of family A is shown in the Appendix. The descendants of individuals II-2 and II-3 were available for testing and the HLA types are shown in Table 11.2.

TABLE 11.2. HLA TYPES OF THOSE FAMILY MEMBERS THAT WERE TESTED

Pedigree number	HLA Haplotypes					
	A	B	C	A	B	C
III-3	30;	14;	-	28;	w53;	w4
III-5	30;	14;	-	28;	w53;	w4
III-7	30;	14;	-	28;	w53;	w4
III-9	2;	w58;	w6	2;	37;	w6
III-14	30;	14;	-	28;	w53;	w4
III-15	2;	44;	-	3;	47;	-
III-16[b]	2;	w58;	w7	28;	w70;	w7
III-17	30;	14;	w8	2;	35;	w4
III-18[b]	2;	w58;	w7	28;	w70;	w7
III-19	w33;	7;	w6	23;	44;	w4
III-20[b]	2;	w58;	w7	28;	w53;	w4
III-21	3;	W70;	w2	24;	w61;	-
III-25	24;	35;	w4	1;	8;	w7
III-30[b]	2;	44;	w5	w33;	w42;	-
III-31	2;	8;	w7	11;	35;	-
III-32	26;	w58;	-	w33;	w42;	-
IV-17	2;	w58;	w7	2;	37;	w6
IV-19[b]	2;	w58;	w7	2;	37;	w6
IV-20[b]	2;	w58;	w7	2;	w58;	w6
IV-21[ab]	2;	w58;	w7	30;	13;	w6
IV-22	2;	37;	w6	28;	w70;	w7
IV-23[b]	2;	w58;	w7	2;	w58;	w6
IV-24	2;	w58;	w7	1;	7;	w6
IV-25	30;	w58;	w7	28;	w70;	w7
IV-27	2;	44;	-	30;	14;	-
IV-28	2;	44;	-	30;	14;	-
IV-29	2;	w58;	w7	30;	14;	w8
IV-30	2;	35;	w4	28;	w70;	w7
IV-31	2;	w58;	w7	w33;	7;	w6
IV-32	w33;	7;	w6	28;	w70;	w7
IV-33	2;	w58;	w7	23;	44;	w4
IV-34[bc]	3;	w70;	w2	28;	w53;	w4
IV-35	2;	w58;	w7	24;	w61;	-
IV-36	2;	w58;	w7	24;	w61;	-
IV-38	11;	27;	w3	w33;	w42;	-
IV-41	24;	w57;	w6	25;	w62;	w3
IV-43	24;	35;	w4	2;	14;	w8
IV-45[b]	2;	44;	w5	24;	35;	w4
IV-48	w33;	w42;	-	11;	35;	w4
IV-50[b]	2;	44;	w5	3;	35;	w4
IV-55	2;	44;	w5	2;	8;	w7
IV-56	2;	8;	w7	w33;	w42;	7
V-15	2;	44;	w5	24;	w57;	w6
V-16	2;	44;	w5	24;	w57;	w6

[a= non-paternity; b= affected individuals; c= recombinant]

The lod scores computed at various recombination fractions between the disease and HLA locus are shown in Table 11.3. For purposes of the calculation, HLA haplotypes in generations I and II could not be postulated, since for the scheme suggested by Ott (1978) to be correct, the genotypes at the HLA locus must be known for all originals. The pedigree was therefore analysed in two parts, with the lod scores calculated separately and then summed, for the descendants of individuals II-2 and II-3 respectively.

TABLE 11.3. LOD SCORES OBTAINED WITH THE MARKERS SITUATED ON THE SHORT ARM OF CHROMOSOME 6.

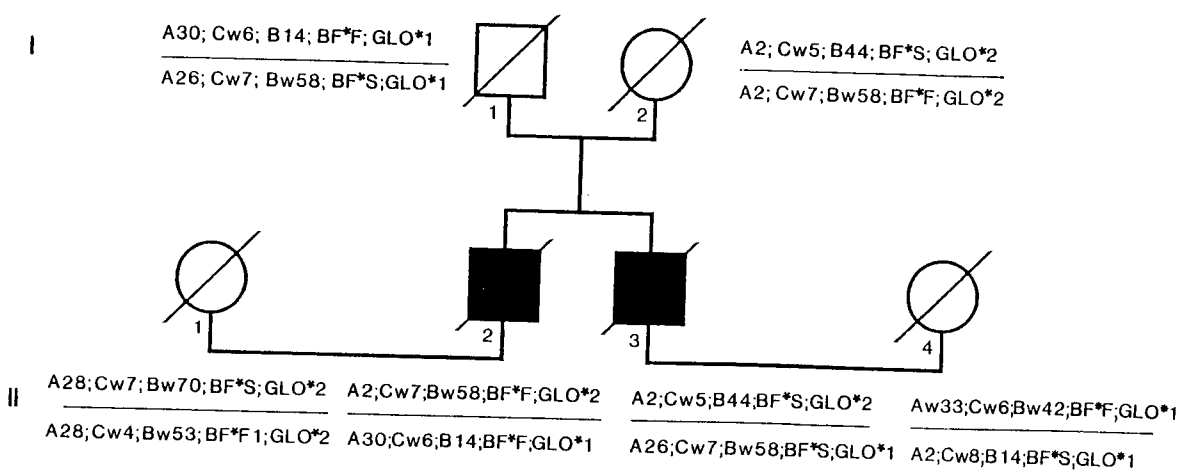
Marker locus	Recombination Fraction (θ) 0.0	0.001	0.05	0.1	0.2	0.3	0.4
HLA	$-\infty$	2.89	4.13	3.93	3.12	2.00	0.74
BF	$-\infty$	-1.97	-0.26	0.04	0.24	0.20	0.08
GLO1	1.62	1.62	1.51	1.36	1.00	0.58	0.19

The total lod score reached a maximum of 4.13 at a recombination fraction of 0.05, indicating the odds to be more than 10,000 to 1 in favour of linkage between HLA and the locus for SCA in this family.

Although individuals in generations I and II could not be typed, it is possible to postulate their HLA genotypes (Figure 11.1). The disease locus is seen to segregate with two different HLA haplotypes in the descendants of individuals II-2 and II-3. There are two possible explanations for this observation. Firstly, recombination between the HLA-A and C loci could have occurred in individual I-2 (assuming heterozygosity at the HLA-A locus). If this is the case, then

the disease allele must have segregated with the HLA-A locus in individual I-2, thus placing the SCA1 locus telomeric to the HLA region. Alternatively, this observation may be the consequence of recombination between the disease locus and the HLA region in individual I-2, who must then have been homozygous for HLA-A2. The chances of the former event having occurred are approximately twice as great as the latter, based on the HLA allele frequencies in this population.

FIGURE 11.1 POSTULATED HLA HAPLOTYPES IN FAMILY A



Postulated HLA haplotypes in generation I and individuals 1 to 4 of generation II. The chances are approximately 2:1 in favour of the recombination in I-2 having occurred between HLA-A and HLA-B rather than between the SCA1 allele and the HLA region. In the former instance, the disease allele would have segregated with the HLA-A locus, placing it telomeric of the HLA region.

The evidence for linkage between the SCA1 and GLO1 locus did not reach the level normally regarded as statistically significant, with the lod score only reaching 1.62 at a recombination fraction of zero (Table 11.3), in spite of presumed double heterozygosity in individuals II-2 and II-3. This is further evidence favouring the telomeric location of the disease locus relative to the HLA region. There is no evidence of linkage between the disease and the BF locus (table 11.3), which is situated in the class III HLA region, but this is because linkage results were not sufficiently informative owing to homozygosity at the marker loci of key family members.

The lod scores generated by the analysis at all other loci are not shown but could be interpreted as follows: linkage with ABO, MNS, RH, FY, ACP1, PGM1, and TF could definitely be excluded while the results with C3, DBP, and HP were in the indeterminate range. The same results were also uninformative due to to homozygosity at the following loci: KEL, ADA, AK, ESD, PGD, PGM2 and CA2.

The results of the linkage analysis using the non-HLA markers in this large family are summarized in table 11.4

TABLE 11.4 RESULTS OF LINKAGE ANALYSIS IN FAMILY A WITH NON-HLA MARKERS

Negative Linkage:	
red cell antigens:	ABO
	MNS
	RH
	FY
red cell enzymes:	acid phosphatase
	phosphoglucomutase
serum proteins:	transferrin
Intermediate Range:	haptoglobin
	C3
	DBP
Uninformative:	adenosine deaminase
	adenylate kinase
	KEL
	esterase D
	phosphoglucomutase 2
	carbonic anhydrase II

11.3.1.2 RESULTS OF LINKAGE ANALYSIS WITH HLA IN FAMILIES B, C, D, E, AND F

The results of the linkage analysis for the HLA markers in the six families are shown in table 11.5.

In the second large family (family B) there was no evidence for linkage to HLA as lod scores below -2.0 are indicative of non-linkage. Similarly in the third family (family C) linkage to HLA was excluded (Lod = -4.50 at θ=0.001). In the last three smaller families (families: D, E, F) there was evidence of probable linkage with lod scores rising at lower recombination fractions (table 11.5.) However, the LOD scores were not sufficiently high to independently confirm linkage in each individual family, because of their size. Despite the fact that these families shared the same phenotype, the validity of summating their lod scores is questionable in light of reports of genetic heterogeneity within the autosomal

dominant spinocerebellar ataxias (van Rossum et al., 1981; Aubuger et al., 1990; Khati et al., 1993)

TABLE 11.5 LOD SCORES FOR HLA MARKERS

Recombination Fraction	0.0	0.001	0.05	0.1	0.2	0.3	0.4
Family no. A	-00	2.89	4.13	3.93	3.12	2.0	0.74
Family no. B	-3.76	-3.33	-0.64	-0.002	0.47	0.5	0.29
Family no. C	-∞	-4.50	-1.18	-0.67	-0.25	-0.09	-0.02
Family no. D	-0.02	-0.02	0.04	0.08	0.09	0.06	0.02
Family no. E	0.18	0.19	0.24	0.25	0.22	0.16	0.08
Family no. F	0.60	0.60	0.54	0.47	0.32	0.17	0.05

LOD SCORES FOR HLA MARKERS

11.3.2 LINKAGE ANALYSIS WITH MICROSATELLITE MARKERS

The number and size of the alleles observed at the 2 loci in the South African background population and in the 5 families with ataxia are shown in Table 11.6.

TABLE 11.6 MARKER ALLELES: NUMBER AND SIZE OF ALLELES IN THE SOUTH AFRICAN BACKGROUND MIXED ANCESTRY POPULATION AND IN THE ATAXIA FAMILIES

MARKERS	ALLELES	
	number	size (nucleotides)
D6S89	11	179-209 bp
D6S260	12	159-179 bp

TABLE 11.7 ALLELE FREQUENCIES FOR D6S89 AND D6S260 IN THE SOUTH AFRICAN MIXED ANCESTRY POPULATION

D6S89		D6S260	
Allele no.	Frequency (percent)	Allele no.	Frequency (percent)
1	5.0	1	17.5
2	15.0	2	5.0
3	17.5	3	2.5
4	2.5	4	10.0
5	10.0	5	10.0
6	17.5	6	2.5
7	7.5	7	12.5
8	7.5	8	5.0
9	10.0	9	20.0
10	5.0	10	2.5
11	2.5	11	5.0
		12	7.5

The specific alleles which segregated with the SCA phenotype in each family at each locus (viz. D6S89, D6S260) are shown in Table 11.8

TABLE 11.8 ALLELES SEGREGATING WITH THE SCA PHENOTYPE

FAMILY	ALLELES SEGREGATING WITH SCA	
	D6S89	D6S260
A	5	7
B	9	5
C	9	5
D	5	7
E	5	7

It is clear from Table 11.8 that the genotypes 5,7 for the markers D6S89, and D6S260, respectively, segregated with the disease in families A, D, E and the genotypes 9, 5 for the same markers segregated with the disorder in families B and C.

The maximum lod scores (at a recombination fraction of 0.00) between the disease phenotype in these 5 families and the microsatelite marker are shown in Table 11.9.

TABLE 11.9 RESULTS OF LINKAGE ANALYSIS BETWEEN SCA AND MICROSATELITE MARKERS D6S89 AND D6S260

FAMILIES	MAXIMUM LOD SCORES (θ = 0.00)	
	D6S89	D6S260
A	7.89	6.41
B	3.89	4.22
C	0.60	1.20
D	1.75	1.17
E	0.90	0.90

The maximum lod scores at a recombination fraction of 0.00 between the disease locus and the 2 microsatellite markers

show that the disease locus in families A and B is on the short arm of chromosome 6. Maximum lod scores at $\theta = 0.00$ for the 3 smaller families were suggestive of linkage of the disorder to the SCA1 locus on 6p. Because of a clear lack of recombinants between the disorder and each of the markers in the families, the genotype combinations (5,7 and 9,5) may be used as haplotypes

11.3.3 TRINUCLEOTIDE EXPANSION AT SCA1

All affected individuals from the 2 large families (A and B) shown to have SCA1 (linked to microsatellite markers; see 11.3.2) had an expanded trinucleotide repeat on one of their alleles. Of the 6 families with the same phenotype as families A and B (but linkage to the SCA1 locus was not proven), 3 were shown to have the expanded CAG repeat (families: C, D, E,). The other 3 families (families F, G, J) did not have the expanded repeat in the affected size range on either of the alleles of the affected persons.

In the 3 families (families: K, N, R) with clinically distinct phenotypes, the expanded repeat was not identified in any of the affected persons. An example of an autoradiograph indicating the size and distribution of the expanded repeats on the alleles of affected individuals with the disease from a subset of the families shown to have SCA1 is shown in Figure 11.1.

The normal alleles range in size from 19 to 36 CAG repeat units. Over 95% of the normal alleles contain from 25 to 33 CAG repeat units, the majority (65%) of which contain 28-30 repeats. The mean repeat lengths for the South African

populations were 29,4 CAG repeat units. The mean size of a repeat on normal chromosomes does not vary significantly among different ethnic populations studied (Ranum et al., 1994). The number of CAG repeats found at SCA1 in affected individuals was always greater than the number of repeats on normal chromosomes, ranging from 46 to 64 with a mean of 52.30.

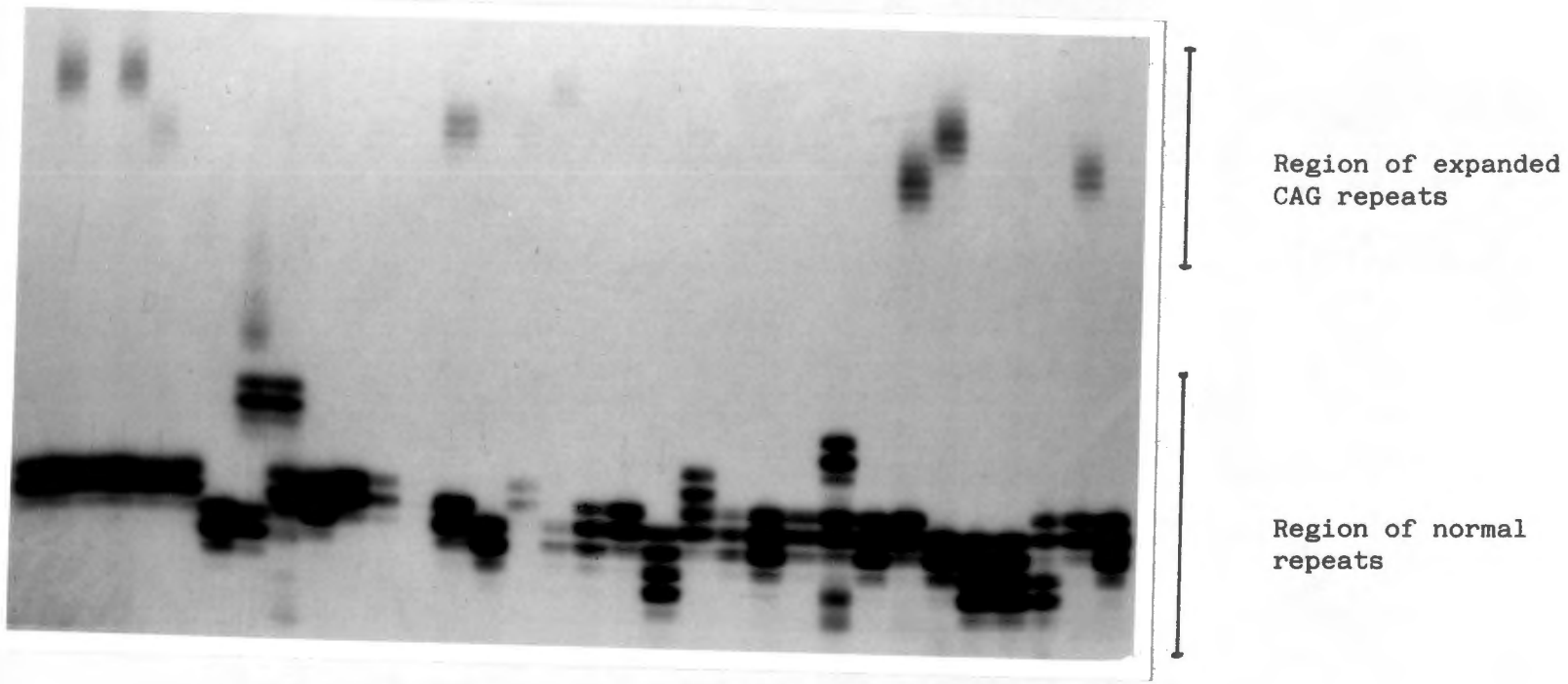


FIGURE 11.2 AUTORADIOGRAPH INDICATING EXPANDED TRINUCLEOTIDE REPEATS

In the South African ataxia families the age of onset is inversely correlated with the CAG repeat size (see Figure 11.3). A linear correlation coefficient r=-0.7069 ($p< 0.01$) was obtained indicating that nearly 50% ($r^2=0.4997$) of the variation in the age of onset can be accounted for by the size of the (CAG)n repeat length. A square root and a logarithm transformation of the age of onset did not improve the correlation coefficient (age of onset square root r= 0.7099 $p<0.01$ $r^2= 0.5039$; age of onset logarithm r= 0.7108 $p<0.01$ $r^2= 0.5052$).

The correlation was obtained between severity of the disease, as measured by duration of illness (age-at-dependency minus age-of-onset), and the number of repeats (see figure 11.4). A correlation of r= -0.3913 ($p>0.05$) was obtained where n=11, suggesting that approximately 15% ($r^2=0.1531$) of the variation in the duration of the disease is due to the number of CAG repeats. The size of this latter sample is too small to make meaningful conclusions from these figures (ie. concerning the relationship between duration of the disorder and the size of repeats).

Figure 11.3 Correlation between the age of onset and the number of CAG repeats

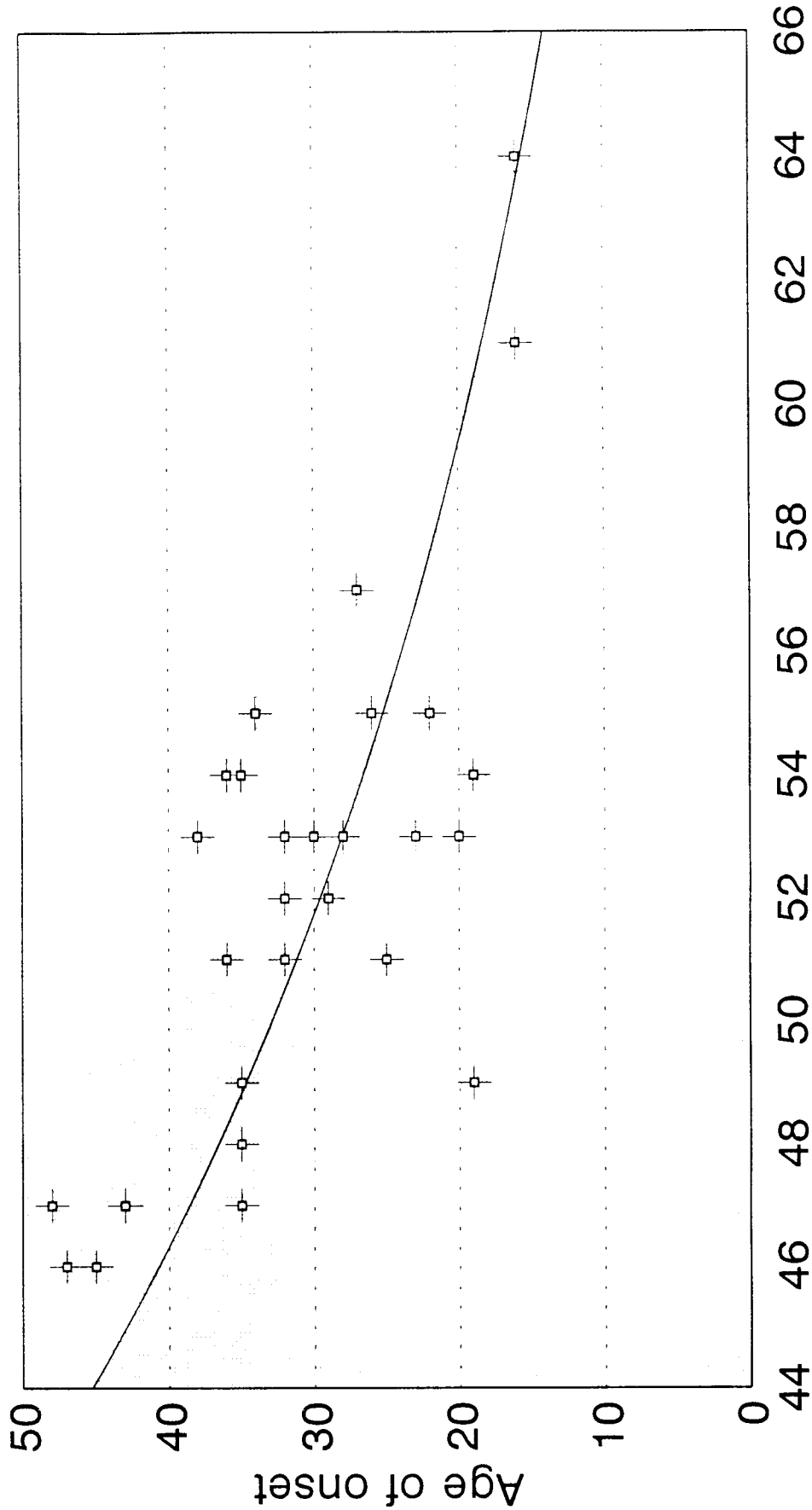
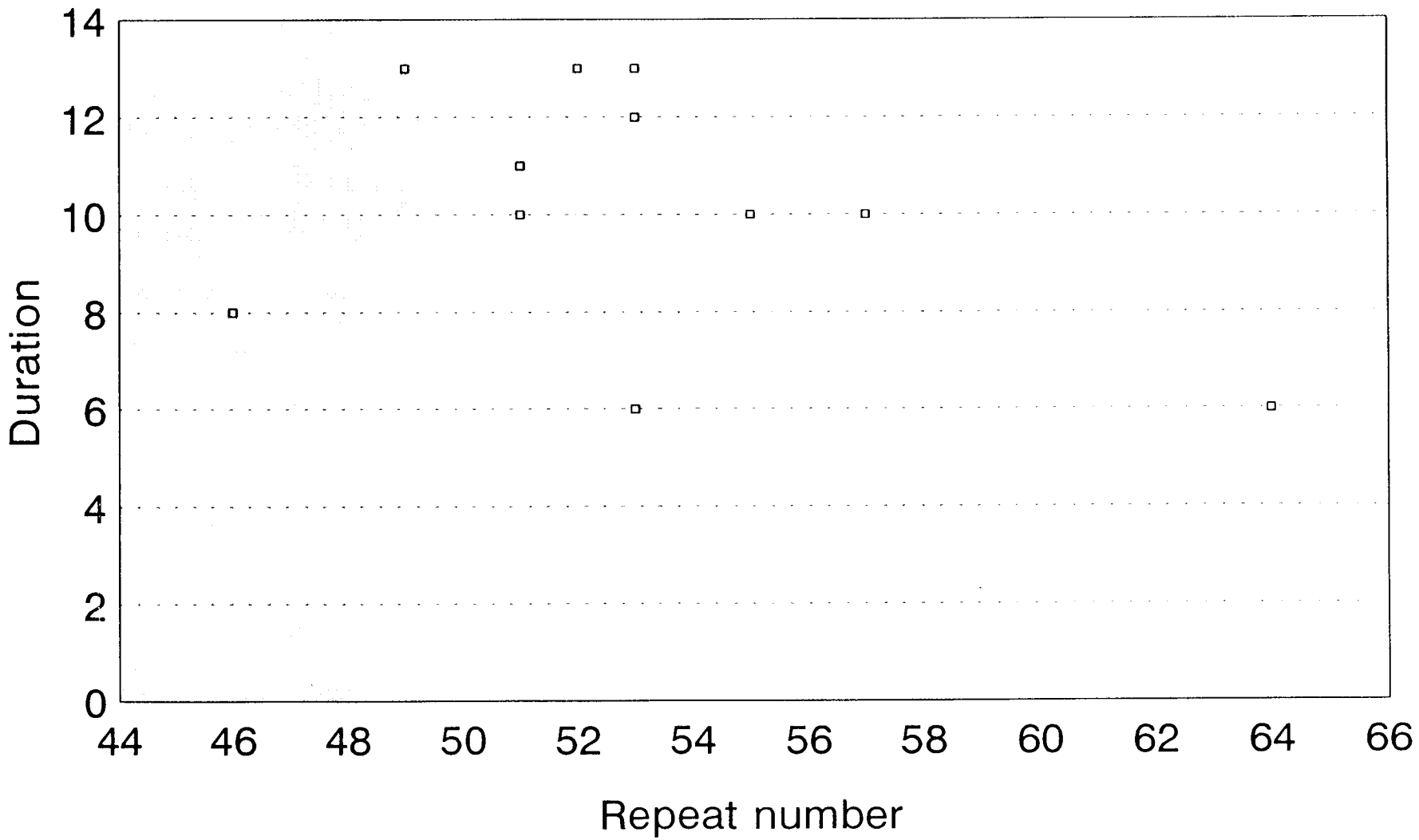


Figure 11.4 Correlation between the duration of the disorder and the number of CAG repeats



11.4 DISCUSSION

11.4.1 HLA ANALYSIS:

This analysis revealed linkage to HLA in one family (family A) only. There was evidence of possible linkage in another 3 families (families: D, E, F) and there was no linkage between HLA and the putative disease gene in one large (family B), and one small family (family C). These observations indicated that the putative gene was located on the short arm of chromosome 6 in one family but the locus of the disease gene in the others remained uncertain. The findings presented here provide support for the concept of genetic heterogeneity in the members of these phenotypically similar South African families with SCA.

The predictive value of HLA typing in Family A was estimated to be 95% on the basis that of 22 individuals in whom disease status could be definitely assigned as either affected or not affected, there was only 1 recombinant between HLA and SCA1. Keats et al. (1991) detected no linkage to HLA in a family which clearly segregated with SCA1, indicating the possibility of a high frequency of recombination between SCA1 and HLA in some families. It is noteworthy that the microsatellite marker, D6S89, was subsequently shown to be very closely linked to SCA1 in some North American families (Zoghbi et al., 1991, Ranum et al., 1991, see 11.4.2). In the light of these findings, HLA linkage alone was not considered to be

sufficiently accurate for use as a test for presymptomatic or prenatal diagnosis in this large South African family.

The exact position of the SCA1 locus in relation to the HLA region was not unequivocally determined in this study. Two studies have provided evidence that the disease locus was situated distal to the HLA region on chromosome 6p (Zoghbi et al., 1991; Ranum et al., 1991). A possible interpretation of the results of the South African study is that the SCA1 locus in family A might be located telomeric to the HLA class I region (see 11.3.1.1). Further studies in this kindred using the microsatellite markers (including D6S89) were undertaken in an attempt to provide additional support for the assignment of the locus for SCA1 distal to HLA.

11.4.2 LINKAGE ANALYSIS WITH MICROSATELLITE MARKERS

The preliminary studies showed linkage between HLA markers and the disease phenotype in family A (maximum lod score 4.13 at $\theta = 0.05$). In family B, however, the exclusion of the disease locus from at least 11 cM on either side of HLA (maximum lod score 0.5 at $\theta = 0.30$) indicated locus heterogeneity between the two kindreds. Tight linkage, however, between the disease locus and two dinucleotide repeat markers was shown in both families, confirming that these families indeed segregate for SCA1.

The apparent discrepant finding of non-linkage between the disease phenotype to HLA in a spinocerebellar ataxia kindred (as in family B), but linkage to D6S89 has previously been

reported by Keats et al. (1991). These results confirm that the exclusion of linkage to HLA does not rule out the possibility that the disease locus is SCA1.

Linkage between the spinocerebellar ataxia phenotype and the D6S89 locus has been shown in families from North America and Italy (Ranum et al., 1991; Keats et al., 1991; Zoghbi et al., 1991; Zoghbi et al., 1991; Pandolfo et al., 1991; Perischetti et al., 1991; Terrenato et al., 1991). In an Italian study, a common D6S89 allele showed strong linkage disequilibrium with SCA1 in five families in Southern Italy (Terrenato et al., 1991). This finding suggests genetic homogeneity of the SCA1 gene and showed that linkage between SCA1 and D6S89 is tight enough to maintain marker alleles in cis to the mutation through at least 12 generations. A multipoint linkage analysis and haplotypes from recombinants mapped SCA1 between two markers, D6S274 and D6S259, 5-6 cM apart in these Italian families (Jodice et al., 1993). Linkage results and the analysis of recombination events, using 9 large American and Italian families confirmed that SCA1 maps centromeric to D6S89 (Kwaitkowski et al., 1993).

The five South African kindreds reported in the present study are of mixed ancestry and reside within a 200 km radius of Cape Town. Because the natural history and ages of onset did not differ significantly, it was initially suspected that the disorder in these kindreds could have been derived from a common affected ancestor. The D6S89 and D6S260 haplotype results indicate that 2 distinct disease associated haplotypes

occur in the 5 families of mixed ancestry, suggesting independant origins of the disorder in the two subgroups. The linkage of SCA1 to D6S89, and D6S260 markers in the South African families is particularly important in defining a common progenitor in these families, and for confirmation of diagnosis where repeats may be indistinct.
Despite the resolution of earlier apparent genetic heterogeneity with regard to spinocerebellar ataxia and HLA, Auberger et al. (1990) have shown that the disorder in a large Cuban kindred does not map to 6p. Heterogeneity of spinocerebellar ataxia is confirmed by several other reports which show no linkage between D6S89 and the disorder (Pandolfo et al., 1991; Ranum et al., 1992; Lazzarini et al., 1992).

Following extensive mapping studies, Gispert et al. (1993) reported chromosomal assignment of a second disease locus (SCA2) for dominantly inherited spinocerebellar ataxia to chromosome 12q23-24.1 in the Cuban families previously excluded from 6p. These authors provided preliminary data supporting the existence of a third locus (SCA3) on the basis of negative linkage to the interval containing SCA2 for seven French families previously excluded from linkage to SCA1. Sixteen families with Machado-Joseph disease were also excluded from linkage to the locus on chromosome 12q (Silveira et al., 1993)

The precedent for genetic heterogeneity in the autosomal dominant spinocerebellar ataxias, despite their phenotypic similarity, was previously established by exclusion of the

Cuban, French, and Danish families from the SCA1 locus on chromosome 6p (Auburger et al., 1990; Khati et al., 1993; Lunkes et al., 1993).

Locus heterogeneity was presumed in the other types of autosomal dominant spinocerebellar ataxia which were thought to have clinically distinct features. In a family with autosomal dominant pure cerebellar ataxia, Frontali et al. (1992) showed exclusion of linkage between the D6S89 marker and the disease locus. Families with Machado-Joseph disease have also been excluded from linkage to the SCA1 locus (Carson et al., 1992) and the gene for this disorder has recently assigned to the long arm of chromosome 14 (14q24.3-q32) by linkage to the D14S55 and D14S48 loci in five Japanese families (Takijama et al., 1993). These reports indicate that genetic heterogeneity underlies the phenotypic differences within this group of disorders.

The lack of recombination between the microsatellite markers and the disease phenotype in the two large South African families supports the localization of the SCA1 gene close to these markers. Maximum positive lod scores at a recombination fraction of 0.00, in the three smaller families, which also share relatively rare haplotypes with the 2 larger families, strongly suggests locus homogeneity in these 5 South African families.

11.4.3 TRINUCLEOTIDE EXPANSION AT SCA1

Expansion of a CAG repeat was observed in all affected individuals from 5 of the 11 South African families investigated by PCR analysis. In these persons the age of onset is inversely correlated with CAG repeat size and individuals with large repeats tend to have an earlier age of onset. Similarly, CAG repeat size also correlates with the severity of the disease; persons with a more rapidly progressive illness tend to have a larger repeat size. These findings parallel those seen in Huntington disease and X-linked spinobulbar muscular atrophy, both of which are progressive neurodegenerative disorders. The mutational mechanism involves an unstable expanded trinucleotide repeat mutation and a definite or putative polyglutamine tract in the encoded protein (La Spada et al., 1991; Orr et al., 1993; Huntington disease research group, 1993). The precise role of the trinucleotide expansion in the pathogenesis of SCA1 remains to be determined; Orr et al.(1993) have hypothesized that all three disorders involve gain-of-function mutations related to the expansion of the repeats. Recent data indicate that repeat instability at SCA1 is more complex than a simple variation in repeat number (Chung et al., 1993).

The identification of an expanded repeat at SCA1 provides a means for rapid genotype analysis of families with autosomal dominant inherited ataxia to determine which families have SCA1. Detection of the repeats in the 3 smaller families (C,D,E) supported the notion of locus homogeneity suggested by the results of microsatellite linkage analysis.

11.5 CONCLUSION

The results of the molecular studies outlined in this chapter document genetic heterogeneity within the South African kindred with familial ataxia. Furthermore, genetic heterogeneity is confirmed within those families with the same phenotype (viz. autosomal dominant cerebellar ataxia type 1, Harding). This observation provides strong evidence against a single founder effect. In those families with SCA1, molecular techniques now provide an accurate and practical approach to the genetic management of the disorder through prenatal and presymptomatic testing.

SECTION VI

PSYCHOLOGICAL SURVEY

Chapter 12 PSYCHOLOGICAL AND SOCIAL PERSPECTIVES

CHAPTER 12 PSYCHOLOGICAL AND SOCIAL PERSPECTIVES

"Then out of the blue the thought came to me that it wasn't impossible for me to develop my father's sickness. How I managed to cope with the subsequent terror and blackest despair is a mystery to me. I started watching myself mercilessly for signs of the disease. I checked my movements, the way I walked, handled things (objects), talked. This left me with an excruciating tension. I walked around in a constant depression. At the age of 16 when other kids were worrying about acne, I was thinking about suicide. I have been working with a psychiatrist for 3 years and I am still unable to reduce in any way the tension that I referred to earlier. He feels that a large part of my problems is my lack of self-esteem and I do agree with him. But on the other hand if a psychopathic killer is holding a gun to your head (nature is often referred to as just that) and threatened to pull the trigger then I think you are quite justified in being a nervous wreck after some time."

Extracts from letter to author from an affected individual.

		page
12.1	Introduction	192
12.2	Methods	194
12.2.1	Questionnaire design	194
12.2.2	Procedure	198
12.2.3	Sample	199
12.3	Results	202
12.3.1	Psychological impact on unaffected persons	202
12.3.2	Risk awareness of unaffected individuals	205
12.3.2.1	General risk awareness	205
12.3.2.2	Personal risk awareness	205
12.3.3	Preselection	207
12.3.4	Attitudes towards affected family members	208
12.3.5	Attitudes towards unaffected family members	209
12.3.6	Somatic complaints in unaffected individuals	209

12.3.7 Attitudes of unaffected persons to reproduction 210

12.3.8 Interviews with spouses 211

12.4 Discussion 212

CHAPTER 12

PSYCHOLOGICAL AND SOCIAL PERSPECTIVES

12.1 INTRODUCTION

Throughout the clinical survey it was apparent that the disorder had a major psychosocial impact on unaffected persons as well as their affected kin. Numerous anecdotes from family members led to the investigation of these issues on a broader scale. Although many affected individuals previously had contact with medical personnel because of their illness, it appeared that many knew nothing of the risk of transmitting the disorder to their offspring. Other affected persons did not seek medical attention when they developed symptoms of the disorder as they knew that the condition was familial and that there was no specific treatment. Few unaffected relatives sought genetic counselling and it was uncertain how well informed they were with regard to their personal risk.

In order to illuminate the plight of these individuals a few general observations and anecdotes are briefly mentioned. A number of affected individuals reported symptoms of anxiety and depression which they attributed to their disease, four of whom required long-term psychiatric therapy for these problems. One person whose symptoms started at the age of 16 years, had attempted suicide on two occasions. She became socially isolated and was reluctant to leave her home because

"people say I am drunk". Marital discord often occurred when a spouse developed signs of this illness.

One large family (family B) lived in a rural area of the Western Cape where the community nursing sister had established contact with members of the different branches of this family. She reported a high percentage of somatic complaints among unaffected individuals, many of whom were poorly informed about the disorder. The survey outlined in this chapter was planned in response to a request from the community nursing sister in order to identify and address these issues. The objectives of the survey are listed below:

1. Assess the psychosocial impact of the disease on both affected and unaffected individuals.
2. Assess the risk awareness amongst unaffected individuals.
3. Assess attitudes of the unaffected relatives towards their affected kin.
4. Assess the problem of somatic complaints amongst unaffected patients.
5. Evaluate attitudes of both affected and unaffected individuals towards reproduction.
6. Investigate strategies within the family for coping with the disorder.

12.2 METHODS

12.2.1 QUESTIONNAIRE DESIGN

On the basis of the anecdotal reports and frequent communications with the community sister, 12 questions were formulated independently by two investigators (the author and a clinical psychologist). It was necessary to formulate the questions ab initio as no previous studies of a similar nature have been undertaken on any of the South African families with hereditary ataxia. Because of the limited information and the uncertainty concerning peoples attitudes towards the disease, the questions were structured in an open-ended format except for those pertaining to somatic complaints. The following questions were posed:

QUESTIONNAIRE:

1. How did the family illness influence your life?
2. What do you think is the biggest problem for:
   a) the person with the illness
   b) the family
3. Who in the family do you think will get it?
4. Why do you think so?
5. Did anybody ever say that you would get it?
6. Who, and why did they say so?
7. Do you think that you will get it, or that you already have it?
8. Why do you think so?

9. How do you feel if you think of, or look at your mother/father/brother/sister, or any other family member who has it?
10. And about those who are healthy?
11. Have you ever had any of the following problems? How often?:
    a) Headaches
    b) Stomach aches
    c) Tearfulness
    d) Difficulty sleeping
    e) Nervousness
    f) Moodiness
    g) Any other problems
12. Do you want any more children:
    a) If yes, how many?
    b) If no, why not?

Question 1 attempts to quantify the psychosocial impact of the disorder on the unaffected family members.

In the analysis, a score was assigned by the investigators to the response of this question : 0 = no effect; 1 = don't know; 2 = moderate effect; 3 = major effect; 4 = positive effect (see 12.3.1). There was agreement between the 2 raters who scored the responses to this question.

The response to question 2 indicates the individual's perception of the major problems which face the affected person and their family. The investigators assigned the responses to the following descriptive categories:

1 Physical disability (ie. physical disability due to impaired walking, speech or limb coordination).
2 Cognitive disability (ie.symptoms of dementia)
3 Emotional problems (disorder of mood or behaviour).
4 Occupational disability (eg.loss of income).
5 Social problems (eg social stigma/embarrasment).
6 Burden to the family (ie.unaffected members have to care for affected persons).

Questions 3 to 8 concern risk awareness. In this family the condition is inherited as an autosomal dominant trait with full penetrance.

All unaffected individuals were assigned a risk status by the author based on criteria shown below:
Low risk status: this was assigned to unaffected individuals in whom a grandparent was affected, but the parent was unaffected and over the age of 49 years (clinical data in this family indicate a range of age of onset from 16 yrs to 49 yrs - see chapter 8). A low risk status was also assigned to individuals in whom both parents and grandparents were unaffected, but in whom a great aunt or great uncle had the disorder.
Intermediate risk status: this was assigned to unaffected individuals in whom a grandparent was affected and the parent was unaffected but less than 49 years of age.
High risk status: this was assigned to unaffected individuals who had an affected parent (ie. 50% risk).

Question 3 evaluates whether family members are aware that certain unaffected members carry a risk of developing the condition. Question 4 probes the insight and perception of risk awareness amongst family members. Questions no 7 and 8 probe the insight and accuracy of perceptions concerning personal risk for developing the disorder.
The response to these questions was analysed and the "perceived" risk status of these individuals was categorized as follows:
1) no risk 2) possible risk 3) high risk. Possible risk included uncertain or ambiguous responses.

In this analysis the "assigned" risk status (i.e."true" risk) of each person was compared to the "perceived" risk status. The "assigned" risk category was determined solely on clinical data from the study of the pedigree. At the time of this survey, molecular data concerning risk status were not yet available for these persons. Furthermore, the objective of the survey was to evaluate the accuracy of the individual's "perceived" risk status as an indicator of the effectiveness of any previous genetic counselling to some members of the family. Since all prior genetic counselling by medical or paramedical personnel was based on clinical data only, it would be invalid to use molecular data to determine an "assigned" risk for the purpose of this comparison.

Questions numbers 5 and 6 probe the issue of preselection as a coping strategy in familial ataxia. Preselection refers to the "sick"-role assignment given to an asymptomatic individual in

a family in which a genetic or other disorder with multiple uncertainties occurs. The selection process is made often when the preselected person is still a child, without knowledge of who will eventually be affected. The process requires the collusion of family members for its initiation and maintenance and serves as a major coping strategy to reduce or bind the stresses and anxieties engendered by uncertainty. This type of selection has been reported in some families in which Huntington disease occurs and the phenomenon is promoted by the delayed age of onset of the disorder and uncertain gene status of the person at risk (Kessler, 1988).

Questions 9 and 10 evaluate personal attitudes towards affected and unaffected persons. Question 11 probed the prevalence of somatic complaints in unaffected individuals. Question 12 assessed the attitudes of unaffected and affected individuals towards reproduction (7 of these persons were younger than 16 years of age and were not asked this question).

12.2.2 PROCEDURE

The study was planned jointly with the community nursing sister. She was able to liaise with family members and relay information to the author concerning their expectations and willingness to participate in the survey. Informed consent was obtained for the survey. Prior to administering the questionnaire, all participants were personally informed by the author of the objectives of the survey. Thereafter, the participants were interviewed individually by two

investigators. The questionnaire was bilingual (English and Afrikaans) and all participants were interviewed in their mother-tongue. Caution was exercised not to ask any leading questions when probing responses.

12.2.3 SAMPLE

Forty volunteer subjects participated in the study. Thirty persons were unaffected (all examined by author) and 6 were affected. Four spouses of affected persons were also interviewed and their responses were analysed separately. The mean age and sex of the sample are indicated in table 12.1

TABLE 12.1 AGE AND SEX OF SAMPLE (excluding spouses)

	Affected persons	Unaffected persons
Male	4	16
female	2	14
mean age	40 yrs	24 yrs
	r: 37-47 yrs	r: 12-35 yrs

[r= range; yrs= years]

The educational level of the persons in the sample was ascertained. The mean standard achieved at school was: Standard 7.27 in the unaffected group (range :4-10) ; and Standard 6.50 in the affected group (range 4-10). Three persons had tertiary education.

The occupational levels of the persons in the sample appear in table 12.5. Six categories were identified: Unemployed;

Unskilled (eg. labourer); Semi-skilled (eg. factory worker); Skilled (eg. clerical); Professional (eg. nurse,teacher); Scholars.

TABLE 12.2 OCCUPATIONAL LEVEL OF THE PERSONS IN THE SAMPLE

	affected	unaffected
unemployed	5	3
unskilled	0	1
semi-skilled	0	10
skilled	1	2
professional	0	2
scholars	0	12

The assigned ("true") risk status of the 30 unaffected persons is illustrated below in table 12.3 :

TABLE 12.3 ASSIGNED RISK STATUS OF UNAFFECTED PERSONS

Risk category	no. of persons	%
low risk	7	23.3
intermediate risk	4	13.3
high risk	19	63.3
total	30	

FIGURE 12.1 FOUR OF THE PARTICIPANTS IN THE SURVEY

12.3 RESULTS

12.3.1 PSYCHOSOCIAL IMPACT ON UNAFFECTED PERSONS

Table 12.4 indicates the impact of the disorder on the lives of the unaffected persons interviewed.

TABLE 12.4 PSYCHOSOCIAL IMPACT OF THE DISORDER ON THE LIVES OF UNAFFECTED PERSONS

Effect	Number	Percentage
No effect	2	6.7%
Uncertain	6	20.0%
Moderate negative effect	5	16.7%
Major negative effect	15	50.0%
Positive effect	2	6.7%

The 2 individuals who felt that the presence of the disorder had a positive effect on their lives cited religious conviction and the desire to support one another ("in the beginning I ignored the disease, but I became positive through religion"; "we were not close but I now feel we must support each other").

Table 12.5 indicates the perceptions of the unaffected and affected individuals concerning the major problems which face affected family members (i.e. response to question 2).

The majority of both affected and unaffected family members perceived physical disability to be the major problem facing the affected members.

TABLE 12.5 PROBLEMS FACING AFFECTED INDIVIDUALS

	affected persons		unaffected persons	
Disability	No.	%	no.	%
Physical	5	83	18	60
Cognitive	0	0	5	17
Emotional	2	33	4	13
Occupational	1	17	2	7
Social	1	17	4	13
Burden to family	0	0	6	20

Two affected members identified emotional lability as a major problem for them. They tended to cry easily and expressed fear and concern that their children might develop the disease. Unaffected individuals (4 persons) observed that affected persons were not infrequently short-tempered and prone to bouts of depression.

Five of the unaffected persons believed that cognitive decline ("can't think properly","the mentality becomes like that of a child") was a problem for some of the affected individuals. None of the affected individuals made this observation. Only 3 people (1 affected, 2 unaffected) mentioned loss of income as a problem. Social problems concerned only 14% of the total sample (1 affected, 4 unaffected). They described a sense of social isolation ("do not feel part of the family") and embarrassment (eg. affected persons falsely accused of being drunk when seen in public places).

Six unaffected individuals felt that a major problem for more severely affected persons was their inability to care for themselves. This placed a burden on the unaffected relatives who had to assist them. None of the affected persons reported being a burden to their family.

Table 12.6 indicates the perceptions of family members concerning the major problems which face the family of an affected person.

TABLE 12.6 MAJOR PROBLEMS FOR FAMILIES OF AFFECTED INDIVIDUALS

	affected persons		unaffected persons	
Problem:	No.	%	no.	%
Emotional	1	16.7	11	36.7
Burden to family	1	16.7	11	36.7
Loss of income	2	33.3	2	6.7

Emotional problems pertaining to the whole family were that they all had to deal with the knowledge that the affected individuals died prematurely and that others may also succumb. Frustration and anxiety were the most common complaints and a loss of religious conviction was reported by a few members. Relatives also had to cope with the emotional lability which developed in some of the affected persons.

12.3.2 RISK AWARENESS OF UNAFFECTED INDIVIDUALS

12.3.2.1 GENERAL RISK AWARENESS:

Ten unaffected individuals believed that no other unaffected relatives were likely to develop the disorder. Eighteen of the unaffected individuals believed that other family members may develop the disorder and 2 unaffected persons were uncertain. They assigned this risk to a parent (5 individuals), a sibling (11 individuals), or an uncle or aunt (2 individuals).
Four of the affected persons believed that others were likely to develop the disorder (all 4 assigned this risk to a cousin), 1 affected person was uncertain and 1 did not believe that any other member would get the disorder. Those individuals who understood the genetic risk for the disorder were uncertain which individuals carried a genuine risk and what the magnitude of the risk was for a particular person. Explanations offered for the assignment of risk to a particular individual related to the physical and emotional characteristics of that person (eg. "has a similar nature to her mother"; "the way he walks"; "he stutters"; "he has a bewildered look";"has a nervous disposition")

12.3.2.2 PERSONAL RISK AWARENESS

All 30 of the unaffected individuals correctly said that they did not have the disorder. Eighteen of the unaffected individuals believed that they would not get the disease, 11 believed that they might get the disorder, and 1 believed that he would get the disorder (see table 12.7).

TABLE 12.7 PERCEIVED RISK STATUS OF UNAFFECTED INDIVIDUALS

	Number	Percent
No risk	18	60.0
Possible risk	11	36.7
High risk	1	3.3

Of the 12 individuals who perceived a positive risk for developing the disorder (ie. high risk and possible risk categories), 3 cited genetic reasons (viz. they knew the disease was inherited but were unsure of the absolute risk), 1 person said that his father had told him that he would get the disease, 5 were uncertain and 2 cited physical problems (eg. pains in the legs and knees) as possible explanations for their perceived risk. Another person believed that she may be able to avoid developing the disorder because she consumed certain calcium powders.

The 18 unaffected persons who believed that they would not develop the disorder frequently offered more than one explanation for this. These included strong religious beliefs (eg."I believe in God and He will not allow it", "I am a child of God"), a lack of any symptoms (eg. "because I am healthy", "I don't get any pains") and a belief that regular exercise or sport would prevent the disease from manifesting. One person believed that the regular application of "Deep Heat" cream to the limbs would prevent the disorder, and another said that he would not develop symptoms because a parent had told him this.

Others offered less specific reasons (eg."I have confidence in myself" and "a feeling that I am not going to get it").

In table 12.8 the assigned (ie."true") risk status of these individuals is compared with their perceived risk status.

TABLE 12.8 "TRUE" VS "PERCEIVED" RISK STATUS

"true" risk category	no.	perceived risk
low risk	7	3 low 4 possible 0 high
intermediate risk	4	2 low 2 possible 0 high
high risk	19	13 low 5 possible 1 high

This comparison of "true" risk to perceived risk indicates that 24 of the 30 unaffected persons had incorrect perceptions of their risk status. It is noteworthy that of the 19 individuals with a high "true" risk status, 13 believed that they had a low risk for developing the disorder.

12.3.3 PRESELECTION

A total of 9 individuals reported that they were told by another person that they would get the disorder. This information was conveyed by a parent (5 individuals), a grandparent (1 individual), a spouse (1 individual) and a cousin (1 individual) and a paramedic (1 individual). In all but one instance it appeared that this occurred sporadically

and no persistent collusion of other family members occurred. Explanations for this warning included: "all the children may get it because it is a family sickness"; "when I am impatient my husband says I will get the illness because my mother was impatient". In one branch of the family in which the parents and 7 unaffected siblings were interviewed, the affected mother and 2 of the siblings each identified the same sibling as likely to get the disease. They cited her nervous disposition which was said to be similar to her mother's as the reason for this increased risk.

12.3.4 ATTITUDES TOWARDS AFFECTED FAMILY MEMBERS

When questioned about their attitudes toward their affected kin, a variety of emotions elicited from the unaffected persons. These included feelings of sympathy, concern, "a sense of duty", "heartache", helplessness, anguish, fear, tearfulness and a sense of "emotional burden". One person wished that a close relative would rather die than suffer in such a way. Another expressed concern at the inability of an affected parent to fulfil parental duties. Others were uncomfortable with the social embarrassment which affected members caused them (eg. strangers often ascribed the manifestations to alcohol abuse). The feelings of fear related not only to the predictable future of the affected persons, but were also evoked by being continually reminded of the potential threat which the disorder holds for the unaffected. The affected individuals expressed very similar feelings towards other affected kin (eg. "pity", "concern", "embarrassment"). Some became anxious because they were

concerned that they would "get as bad as" their affected siblings.

12.3.5 ATTITUDES TOWARDS UNAFFECTED FAMILY MEMBERS

The majority of individuals (both affected and unaffected) expressed a feeling of "happiness" (Afrikaans:"bly") towards those who did not have the disease (eg."happy at their health";"I am happy because it would be terrible if everyone got it"). In some this happiness was tempered by feelings of uncertainty about the future ("those who have the sickness were well at first"). Others felt that those who were spared had responsibilities towards the affected persons and that they were obliged to look after them. One individual commented "I am ashamed for those who are healthy but don't work because my mother, who is sick, still works". Another person was worried that the unaffected persons may be taking something that prevented them from getting the illness and that they were concealing this information from others in the family.

12.3.6 SOMATIC COMPLAINTS IN UNAFFECTED INDIVIDUALS

Seventy percent of unaffected persons reported at least one frequent somatic complaint. Table 12.9 show the prevalence of somatic complaints in unaffected persons.

Other complaints, which probably had a non-psychological origin, included pains in the legs (1 person), asthma (1 person), hayfever (1 person), and a "kidney problem" (1 person).

TABLE 12.9 SOMATIC COMPLAINTS

	affected persons		unaffected persons	
Complaints	No.	%	No.	%
Headache	3	50	11	36.7
Stomach ache	0	0	3	10.0
Tearfulness	2	33	8	26.7
Sleep disturbance	3	50	2	6.7
Nervousness	4	67	12	40.0
Mood swings	2	33	11	36.7

12.3.7 ATTITUDES OF UNAFFECTED PERSONS TO REPRODUCTION

The majority of unaffected persons (69.6%) wanted more children. The attitudes of unaffected individuals towards having further children is shown in table 12.10.

TABLE 12.10 ATTITUDES OF UNAFFECTED INDIVIDUALS TOWARDS REPRODUCTION

	No.	Percent
Want more children	16	69.6
Do not want further children	6	26.1
Uncertain	1	4.4
TOTAL	23	

All 6 unaffected individuals who did not want more children already had children. Only 2 of the 6 unaffected persons cited the risk for the disease as a reason for not having additional children. The other reasons given were financial, physical

(eg.sterilization) and a completed family. Of the 16 individuals who desired additional children, 11 planned on having 2 or more children.

12.3.8 INTERVIEWS WITH SPOUSES

Four spouses (aged 34, 57, 74 and 82) were interviewed. The two older woman were widowed, while the younger woman and man were living with their spouses. The responses of the 82 year old woman were discarded because she was intellectually compromised. The other widow discussed her fears for her one (of eight surviving children) healthy son and rationalized her distress at the recent diagnosis of her daughter who the doctor said "only had it mildly (net in 'n ligte graad)." She thought that the family illness may be divine retribution. The 34 year old pregnant wife, a factory worker, also expressed her fears for her children, especially her 10 year old daughter who suffered from headaches. She empathized with the family members who had the disorder, but added that they were very impatient people. The 57 year old male, a teacher, discussed his frustration, anxiety, insomnia, depression and constant tension, and admitted that the unaffected family members did not always know how to react when the affected person became frustrated and refused help. He was worried that his daughter and one of his two sons, who were slightly built, would get the disorder, and also expressed similar fears for his grandchild. He did not think that his well-built son was at risk. Neither of the married spouses wanted more children.

12.4 DISCUSSION

Relatives of affected persons face problems (viz. physical, social, occupational, "burden to family") common to those who live with and have to care for the chronically ill. The progressive nature of the disease and the dementia which develops in certain members in the later stages of the illness, compounds these difficulties. Furthermore, the genetic nature of the disorder and attendant uncertainty as to who else will develop the disorder adds another dimension to these issues. Most of the unaffected persons had very rudimentary understanding of the genetics of the disease, as explained to them by relatives, and had not previously interacted with genetic counsellors. One third of unaffected persons were uninformed or unaware of the inherent risk that existed for certain unaffected family members. A high percentage (63%) of unaffected persons did not perceive any personal risk for developing the disorder.

In a comparison of "true" risk with "perceived" risk, 80% of unaffected individuals (24/30) had incorrect perceptions of personal risk status. A number of possible explanations may account for these high figures. It is clear that a lack of effective genetic counselling , particularly amongst the unaffected members of this family may account for some of the misconceptions. Religious conviction and psychological strategies such as denial and projection would also help explain this phenomenon. This was evident in the rationalizations which individuals offered (eg."God will not

allow it";"because I exercise";"because I take calcium powders"). Similar findings have been reported in families with Huntington disease:"denial and hope are the twin mainstays of survival in impossible circumstances" (Wexler, 1992).

There was some evidence to support the preselection phenomenon as a coping strategy in only one branch of this family in which 3 members indicated their belief that a particular sibling would develop the disorder in the future. The "preselected" person initially denied that anyone had ever told her she would get the illness but later in the interview expressed her fear of becoming ill because of what she had been told by her family. The strategy of preselection is thought to contain and bind the family's anxiety about the threat of the genetic disorder. It provides the illusion of protection from the disease (viz. it will happen to him, not to me) at the expense of the preselected person (Kessler, 1988).

Unaffected persons had predictable responses (eg. sympathy, concern, duty-bound) towards their affected kin. For some, however, the interaction with affected individuals served as a constant reminder of the potential threat to their own future well-being. For this reason, a few persons tended to avoid contact with affected members. Although many individuals found comfort with their religious beliefs, several had abandoned religion because they could not rationalize why their family should be "cursed with such a disease". Although the

overwhelming attitude towards those who appeared to be spared was positive (eg."glad","happy"), not unexpectedly, feelings of resentment and suspicion were occasionally evident. The high prevalence of somatic and psychologic complaints amongst unaffected persons is a reflection not only of the stress of living and coping with a chronically disabled person, but is also a measure of the personal threat and insecurity which the disease confers. The very high prevalence of symptoms may reflect a fault in the design of the questionnaire in which unlike the other more open-ended questions, the direct questioning about somatic complaints may have pre-empted responses.

The survey revealed that the disorder had little impact on the attitudes of both affected and unaffected persons concerning reproduction. No family member, either at risk or affected, had chosen not to have children because of the disease. The majority of those at risk wanted more children and 2 of the 6 affected persons wanted additional children despite their own disability. These attitudes towards reproduction should be considered in the context of a family in which many members appear to be poorly informed about three important issues viz.: the genetic aetiology of the disorder; which persons carry a high risk for the disease; and the magnitude of the risk for potential offspring.

The survey confirmed the profound psychosocial impact which the disorder has on all family members and identified a variety of issues and misconceptions which must be addressed.

Many factors influence the responses of persons affected with genetic diseases and their families. Greater understanding of these influences and dynamics is required in order to plan effective counselling in the future, particularly now that predictive testing has become a viable option.

SECTION VII

CONCLUSIONS

Chapter 13 CONCLUSIONS, APPLICATIONS AND RECOMMENDATIONS

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		page
13.1	Pilot study	218
13.2	Prospective survey	218
13.3	Diagnostic imaging and electrophysiological tests	219
13.4	Molecular linkage studies	220
13.5	Psychological survey	221
13.6	Practical applications and future objectives	222
	13.6.1 Establishment of Neurogenetics clinic	222
	13.6.2 Future studies	223
	13.6.3 Establishment of a lay support group	224
	13.6.4 Predictive testing	224

CHAPTER 13

CONCLUSIONS, APPLICATIONS, AND RECOMMENDATIONS

13.1 PILOT STUDY

The retrospective pilot study identified 18 families with familial ataxia that had been seen over a 10 year period at Groote Schuur Hospital. Twelve of these families were still living in the area and were subsequently contacted and reassessed prospectively. This study provided the first available data in South Africa on the clinical spectrum, natural history and prognosis of the late onset familial ataxias. A group of individuals with sporadic ataxia was identified and compared with the familial group. Although this group of persons did not form part of the prospective survey, records of all individuals with late onset sporadic ataxia has been kept and a study is planned to examine these individuals (phenotype resembling the familial variety) for the expanded trinucleotide repeat on Chromosome 6.

13.2 PROSPECTIVE SURVEY

This prospective population-based study of the spectrum of late onset spinocerebellar ataxias, was the first to be undertaken for a region of South Africa. The survey provided information concerning the minimal prevalence, mode of inheritance, symptomatology, range of clinical manifestations, course and prognosis of the different phenotypes. In

particular, the most commonly encountered phenotype (adult onset ataxia with retained reflexes, Currier classification) in the Western Cape region of South Africa, is similar to that observed in families in Europe and North America. Information from this clinical survey has resulted in a more accurate and appropriate counselling service at the Neurogenetics clinic, Groote Schuur Hospital. Eight other small families with unusual phenotypes were identified. These show some similarities to reports in the literature, but there were also significant differences. It is uncertain whether genetic heterogeneity or variable expression of the same defect accounts for these observations. This issue will be addressed in future studies.

13.3 DIAGNOSTIC IMAGING AND ELECTROPHYSIOLOGICAL TESTS

The MRI scan study demonstrated the morphological changes of the nervous system present at different stages during the course of the disorder. In the early stages of the illness, clinical symptoms and signs precede any detectable morphologic changes on this scan. Therefore, MRI scans are of limited value as a diagnostic tool at the onset of symptoms, when the clinical diagnosis may be in question. Later on, there was a moderate correlation between the atrophy seen on the scan and the clinical ataxia syndromes.

Similarly, electrophysiologic studies demonstrated that a motor polyneuropathy was a variable and usually late manifestation in persons with adult onset ataxia. Nerve

conduction studies and EMG helped to complete the delineation of the phenotype in those individuals with distinctive ataxia syndromes.

13.4 MOLECULAR LINKAGE STUDIES

Linkage studies have confirmed genetic heterogeneity within the South African families with late onset ataxia. The results with the microsatellite markers, D6S89 and D6S260, indicate that 2 disease-associated haplotypes occur in the 5 families of mixed ancestry, suggesting independent origins of the disorder. Affected members in the five families with ataxia were shown to have an unstable expanded trinucleotide repeat at the SCA1 locus on chromosome 6. This provides a means for rapid genotype analysis of families. A major advantage is that the result can be obtained in an individual if the expanded region is detected, thereby eliminating the need for large family studies. The linkage of SCA1 to the microsatellite markers, D6S89 and D6S260, is important in these families for confirmation of diagnosis, particularly when the repeats are indistinct. In families with SCA1, molecular techniques provide an accurate approach to the management of the disorder through presymptomatic and prenatal testing.

13.5 PSYCHOLOGICAL SURVEY

In contrast to the breadth of literature on the classification, pathology, and genetics of the spinocerebellar ataxias, there is a paucity of reports addressing the emotional and social aspects of the disease (Boutte, 1990). Although this study was undertaken on a relatively small sample of 40 persons, it documents the profound psychological impact of the disorder of unaffected members of the South African families. The most striking feature of the survey was that both affected and unaffected family members had a very poor understanding of the genetic nature of the disorder, even though most affected persons had previously sought medical attention for the condition. The majority of persons interviewed had misconceptions concerning the risk status of unaffected persons. Attitudes towards reproduction were, not surprisingly, unaffected by the presence of the familial disorder. The survey highlights the need for effective genetic counselling and the provision of a support service to help family members understand the genetic implications of the disorder and to cope with their feeling of isolation and despair.

13.6 PRACTICAL APPLICATIONS AND FUTURE OBJECTIVES

13.6.1 ESTABLISHMENT OF NEUROGENETICS CLINIC

A Neurogenetics Clinic was established at Groote Schuur Hospital in 1993. This multidisciplinary clinic runs on the first Thursday in each month and serves the following functions:

1. The diagnosis and care of persons with inherited neurological conditions;
2. Genetic counselling for the affected persons and their relatives;
3 Collection of blood samples for DNA banking;
4 Accurate recording of all relevant pedigrees and the creation of a patient database for the inherited neurodegenerative conditions.

The Huntington disease clinic, which has been running at Groote Schuur Hospital since 1978, has been incorporated into the Neurogenetics clinic. The staff of the clinic comprises 2 neurologists, 2 medical genetic counsellors, and a genetic nursing sister. A psychologist and a social worker are available for consultation.

Numerous lectures and presentations have been given by the author throughout the country on various aspects of this project (abstracts in the appendix). This has helped to increase the awareness of the condition and improve the understanding of the disease and the associated psychological

and social problems that it creates. Although this project was confined to families living in the Western Cape region, numerous referrals of individuals with familial ataxia have ensued from all parts of the country. Where possible, blood samples have been obtained from the relevant persons for DNA banking. In 1988 a management system for DNA banking was installed in the micro-computer network of the laboratory of the Department of Human Genetics, UCT. Details of all persons with familial ataxia whose blood is taken for DNA banking are stored on this program. Confidentiality is an important aspect of spinocerebellar ataxia DNA banking and only authorized staff members are allowed access to this data.

13.6.2 FUTURE STUDIES

A number of future studies are planned. These include:

1) A study of persons with sporadic ataxia, for detection of the unstable trinucleotide repeat;
2) A postmortem study of specimens of different tissue to examine the expression of the expanded repeat in different tissues and specifically in different areas of the nervous system. Recent work on Huntington disease has shown variable expression of the expanded repeat in different areas of the brain (Telenius et al., 1994);
3) Studies to determine the genotype in those South African families not associated with SCA1.

13.6.3 ESTABLISHMENT OF LAY SUPPORT GROUPS

The author has attempted to encourage the formation of a lay support group for families with familial ataxia. In 1986 the Huntington Society of South Africa was formed with the aim of providing affected families with an opportunity to meet one another and to share experiences, discuss problems and act as a support group. Many of the families with familial ataxia and Huntington disease are from lower socio-economic groups, and financial constraints may necessitate combining resources to form a single society to serve the needs of families with either disorder. An important role for the health care worker and the lay society would be to educate the community about the condition, particularly its genetic nature and progressive disability. This would serve to increase awareness and minimize the social stigma attached to the disorder. While many family members expressed common fears, a myriad of individual responses were elicited. This emphasizes the need for individual counselling.

13.6.4 PREDICTIVE TESTING

Plans are currently under way for the introduction of a predictive testing service for spinocerebellar ataxia at Groote Schuur Hospital. A number of problems and ethical issues are being addressed. The principal concern for those involved with predictive testing has been the possibility of serious emotional and psychological effects in people whose results indicate a high risk of having the disease gene, particularly as these results may be available many years

before the onset of symptoms. The persons who receive a positive result may have great difficulty in sustaining goals and maintaining optimism in the face of this knowledge. The test results may have a similar impact on the spouse and may impose strain on the marital relationship. Many of these issues have been addressed in the context of Huntington disease (Huggins et al., 1990, 1992; Bloch et al., 1992; Chapman, 1992). While there have been no catastrophic responses to positive test results in any of the published reports, these predictive tests were all performed in a clinical context that provided pre-test psychiatric and psychological assessment, adhered fully to the principles of informed consent, offered both pre-test and post-test counselling, and included psychological support and follow-up (Chapman, 1992). A study of the consequences of predictive testing for Huntington disease showed potential benefits for the psychological health of persons who receive results that indicate either an increased or decreased risk of inheriting the gene for the disease (Wiggins et al., 1992). Notwithstanding these findings, there is agreement that there are many problems associated with predictive testing and this test should be approached by all parties with the utmost caution, and should not be undertaken without safeguards (Hayes, 1992). A number of centres in the United Kingdom and the United States of America offer predictive testing and different approaches to predictive testing have arisen (Fahy et al., 1989)

The World Federation of Neurology has issued an ethical policy statement for Huntington disease molecular genetic predictive testing. The United Kingdom Huntington Prediction Consortium has also issued a protocol for predictive testing for Huntington disease. These realistic guidelines and recommendations concerning the use of molecular technology for predictive testing in Huntington disease are readily applicable to the late onset ataxias. Both disorders are inherited as autosomal dominant traits, manifest in adulthood, and have a similar course and prognosis. A similar genetic mechanism (ie. an unstable expanded trinucleotide repeat) is responsible for both disorders. Recently Shrimpton et al. (1993) reported their experience of presymptomatic testing for autosomal dominant ataxia (SCA1) in the United Kingdom.

The psychological survey in this project has identified several issues which will be addressed prior to the introduction of a predictive testing service for the familial ataxias in the Western Cape region. Affected persons and their families, particularly in the rural areas require more effective counselling, particularly with respect to misconceptions of risk status and improved understanding of the nature of the disorder. In the future it will be necessary to make optimal use of existing social services. Often financial constraints and lack of transportation for patients and persons at risk have made certain services based in the metropolitan areas inaccessible to some families. This accounts for many of the misconceptions held by members of the

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affected families in the rural area. The relevant community social worker and nursing sisters require education regarding all aspects of the condition so that they are more able to assist in identifying and managing problems facing affected persons and their families. The primary health care worker is often faced with the task of assisting family members to cope with problems of caring for the ataxic patient, informing them of existing services and helping individuals at risk to come to terms with their own status. By educating the family members about the disorder, individuals at risk would be more able to make informed, voluntary decisions about their lives. Within the Groote Schuur Hospital complex, a multidisciplinary team is being assembled (neurologists, genetic counsellor, psychologist and social worker) to formulate and implement a protocol for the support service necessary for predictive testing for familial ataxia (based on WFN recommendations for Huntington disease). The author has attended the Canadian National Predictive Testing meeting in Vancouver in September 1993 and is aware and informed of the cost, pitfalls and resources required to implement and maintain such a service.

The Department of National Health and Population Development, Genetic Service, has been approached for a financial and service commitment for DNA banking and predictive testing. Their support will be vital for the maintenance of an ongoing service. In South Africa the expansion of the practice of modern tertiary care medicine to the interest of individual patients, needs to be balanced by collective measures required at the level of preventative and primary health care in order

to improve the health of future generations. Questions will be raised about the allocation of funds to provide an expensive laboratory service in order to do predictive testing on a disorder which is relatively uncommon in the community when other diseases such as TB are endemic, particularly in the light of reduced state funding of teaching hospitals and the medical research council. Although the late onset ataxias are a relatively rare group of disorders, the extent of the problem will increase with each successive generation aggravating the financial burden of chronically disabled patients to the health system. Predictive testing is within the realms of preventative and primary health care as it provides a practical solution in the genetic management of the disorder and I believe that it merits funding. It will probably not be feasible to establish facilities for predictive testing at more than one genetic laboratory in the country because of the cost in maintaining such a service (considering the number of samples that each lab would be likely to process). A practical solution would be to centralize such a facility to a single laboratory to cater for the needs of the whole country. In certain centres in the United States of America where predictive testing is offered (for Huntington disease), the uptake of the test has been low, even when those who are at risk are systematically informed of its availability (Quaid et al., 1987; Craufurd et al., 1989). Those currently being tested are therefore a self-selected group and those who decline to be tested might be less able to handle the severe stresses entailed (Harper et al., 1990). Predictive testing is, however, enhancing the quality of life

of many at risk individuals. As stated by Chapman (1992), in this way they are freed from the burdens of the unknown, provided with more certainty in their lives, and given a greater sense of control over decisions involving their educational and career choices, marriage and family planning.

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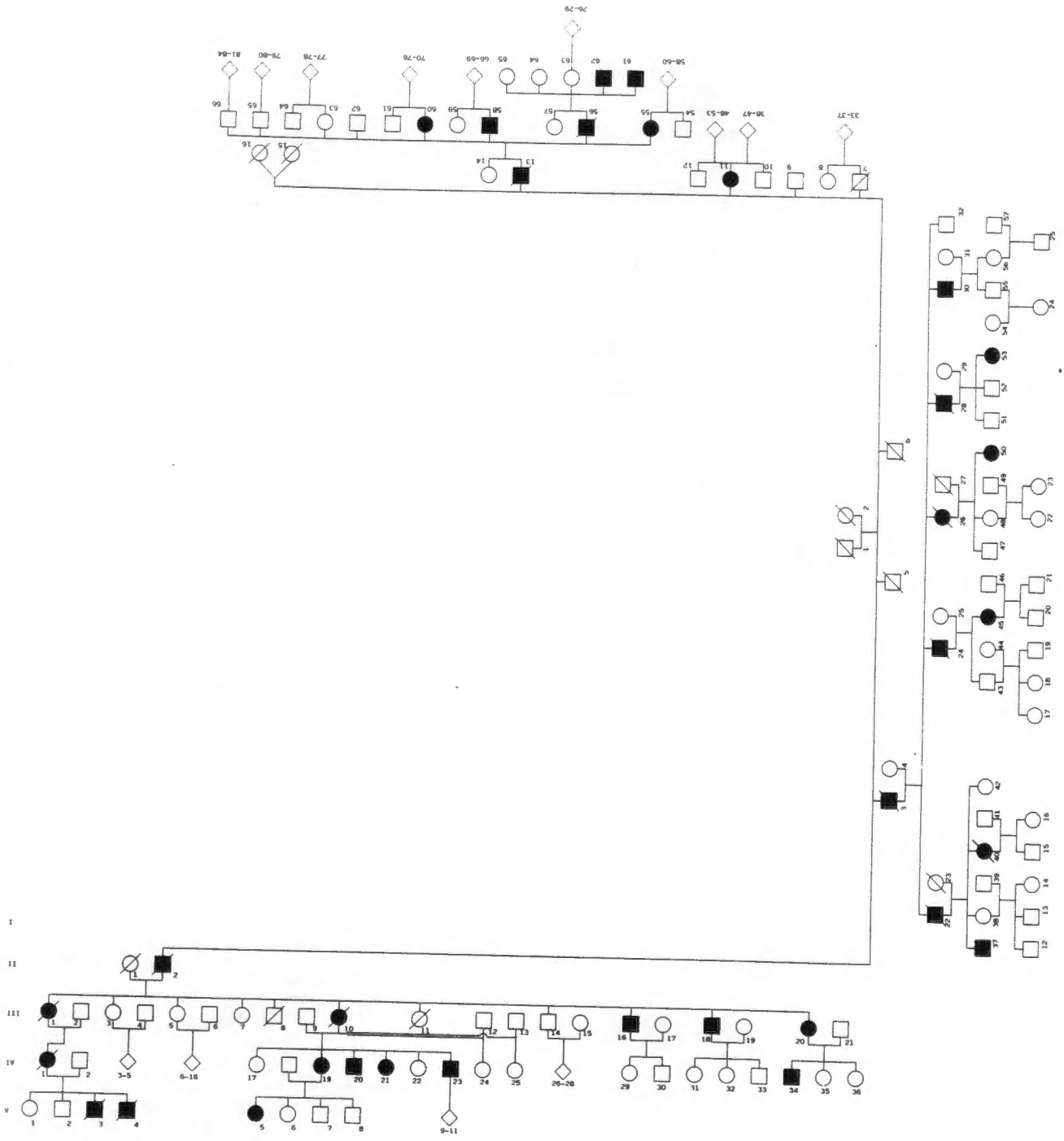
APPENDIX

A1.1	Pedigrees	
	family A	ii
	family B	iii
	families C and D	iv
	families E and F	v
	families G and H	vi
	families I and J	vii
	families K and L	viii
	families M and N	ix
	families O and P	x
	families Q and R	xi
	families S, T, U, V, W, and X	xii
A1.2	Protocol for Clinical Examination	xiii
A1.3	Publications and Abstracts relating to this thesis	xv

Family A



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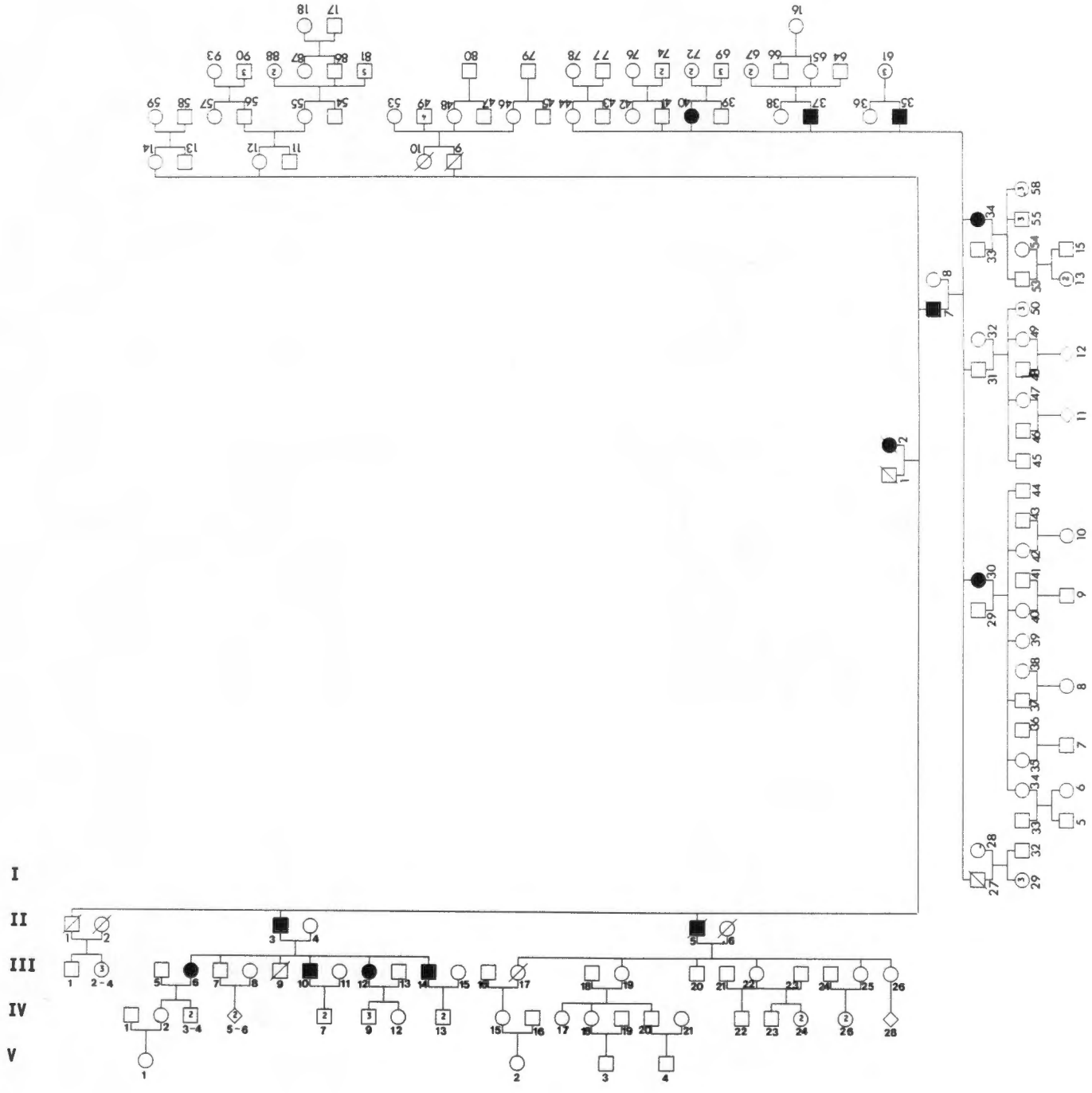

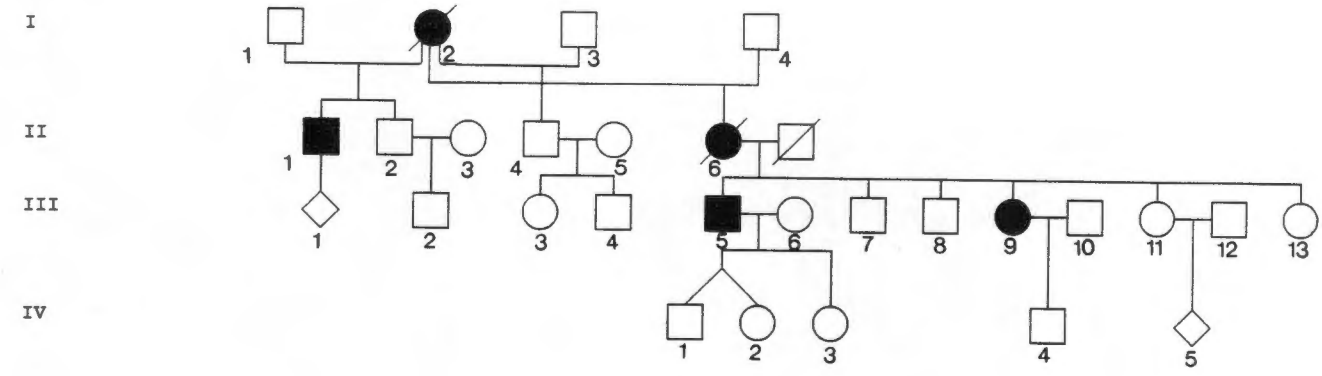

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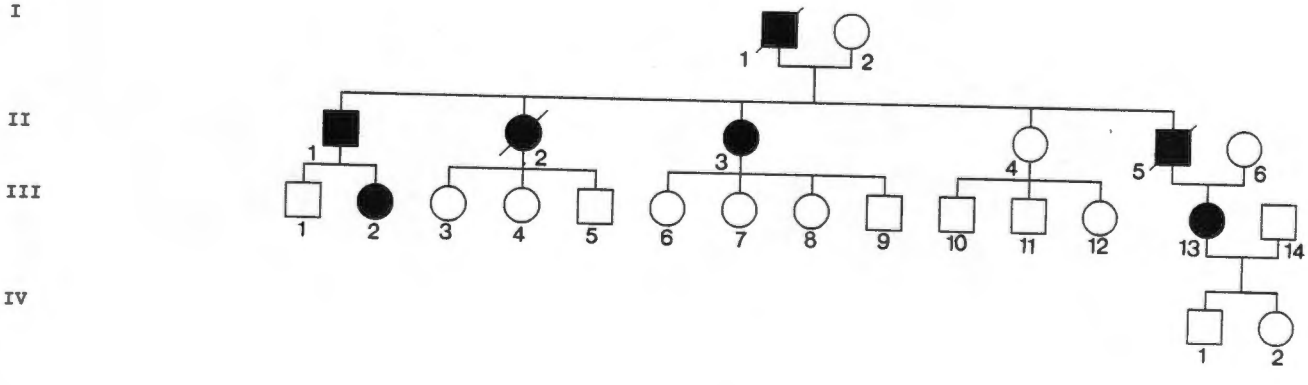

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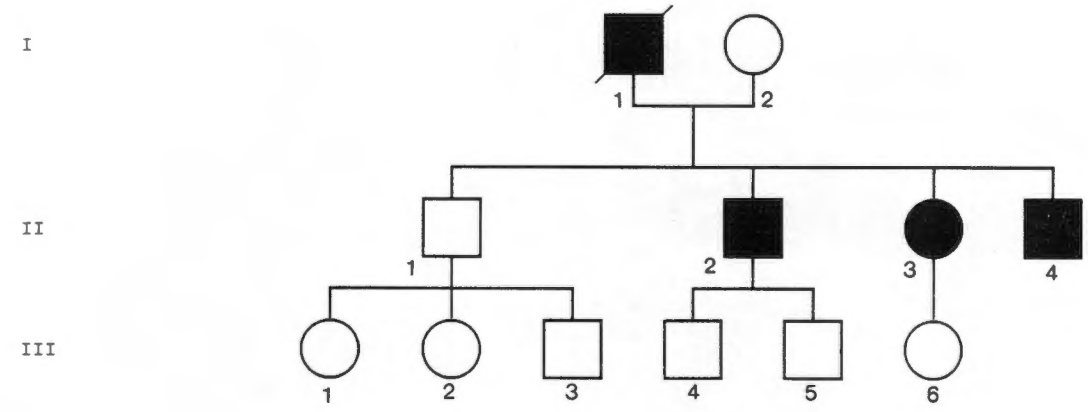

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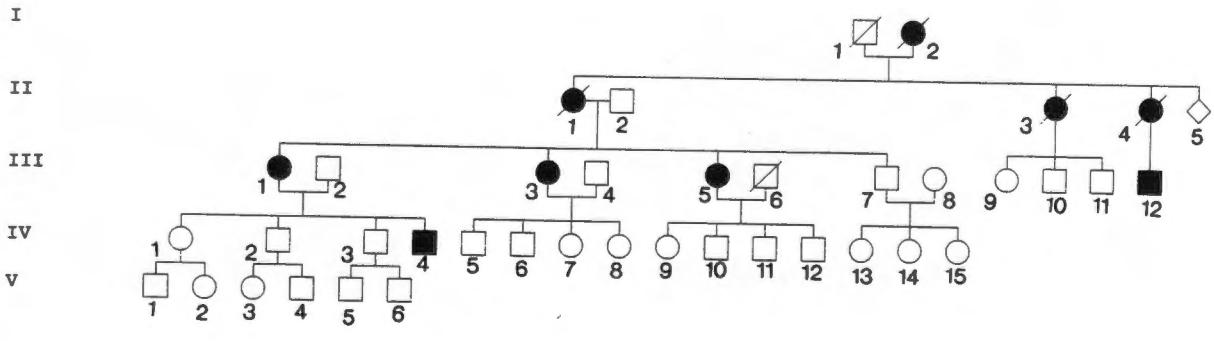

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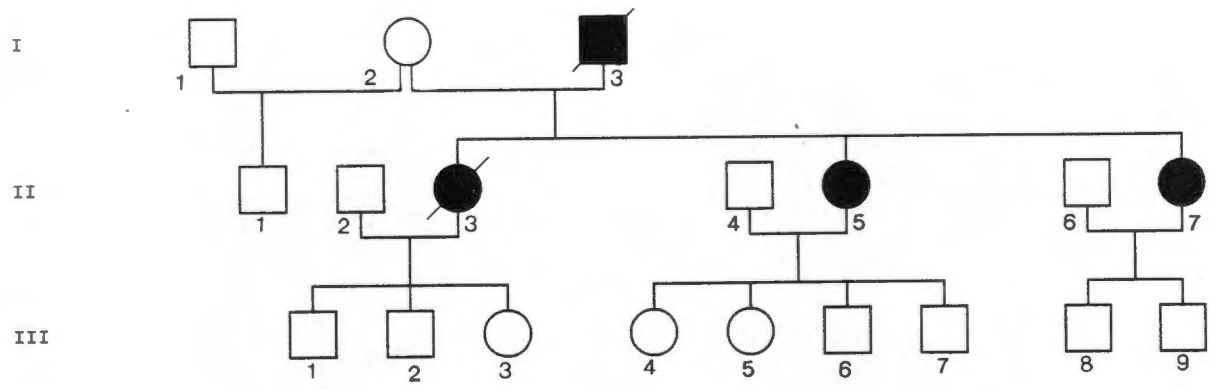

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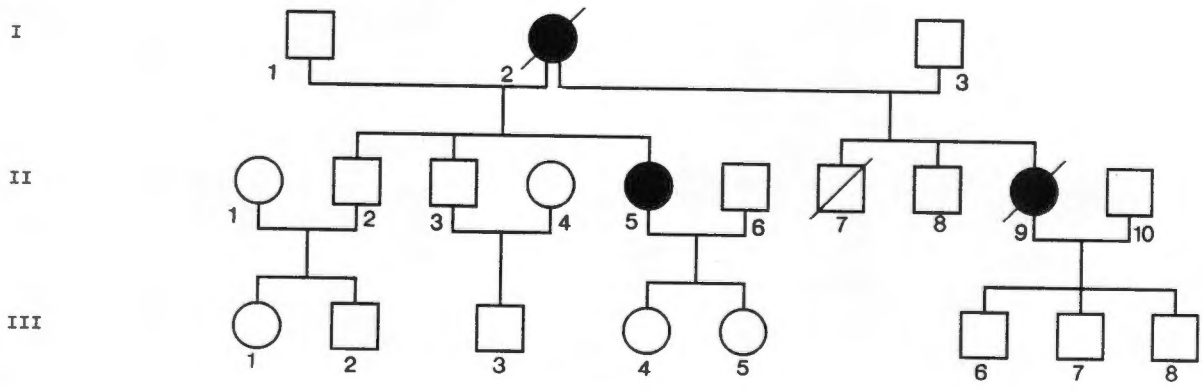

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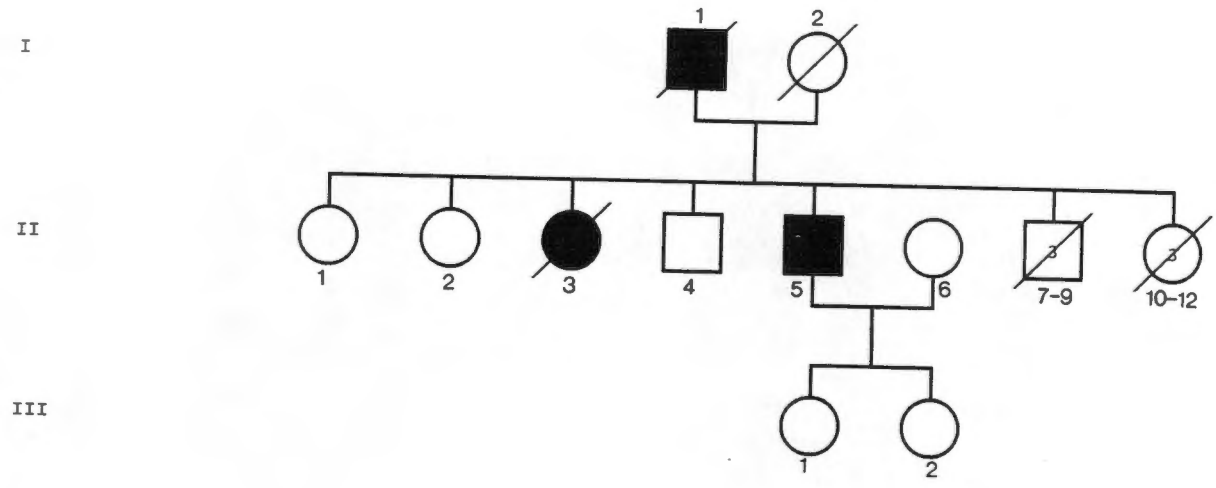

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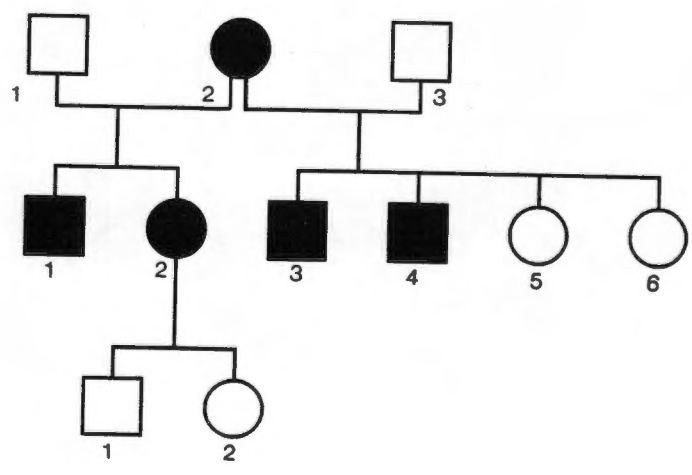

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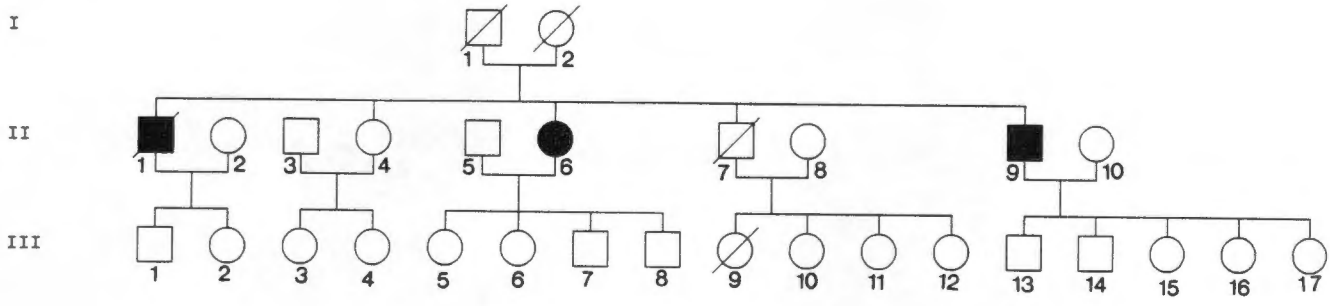

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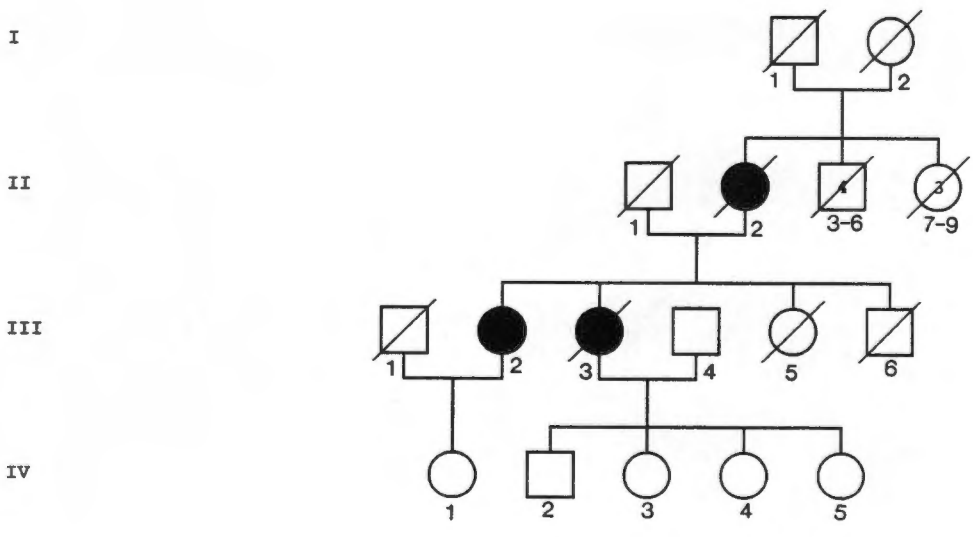

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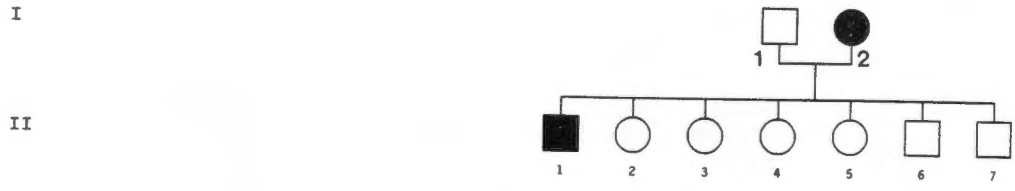

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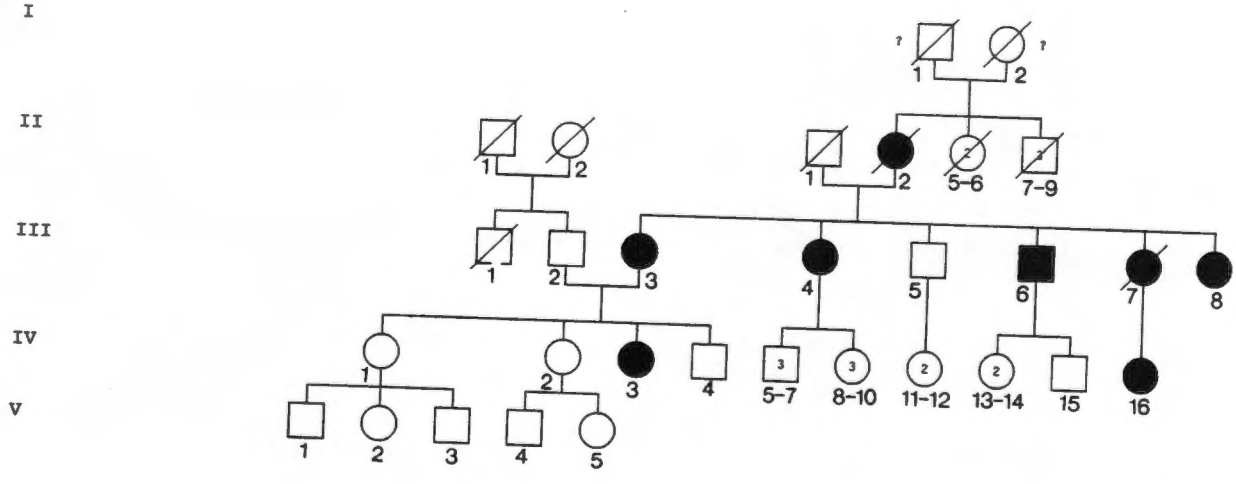

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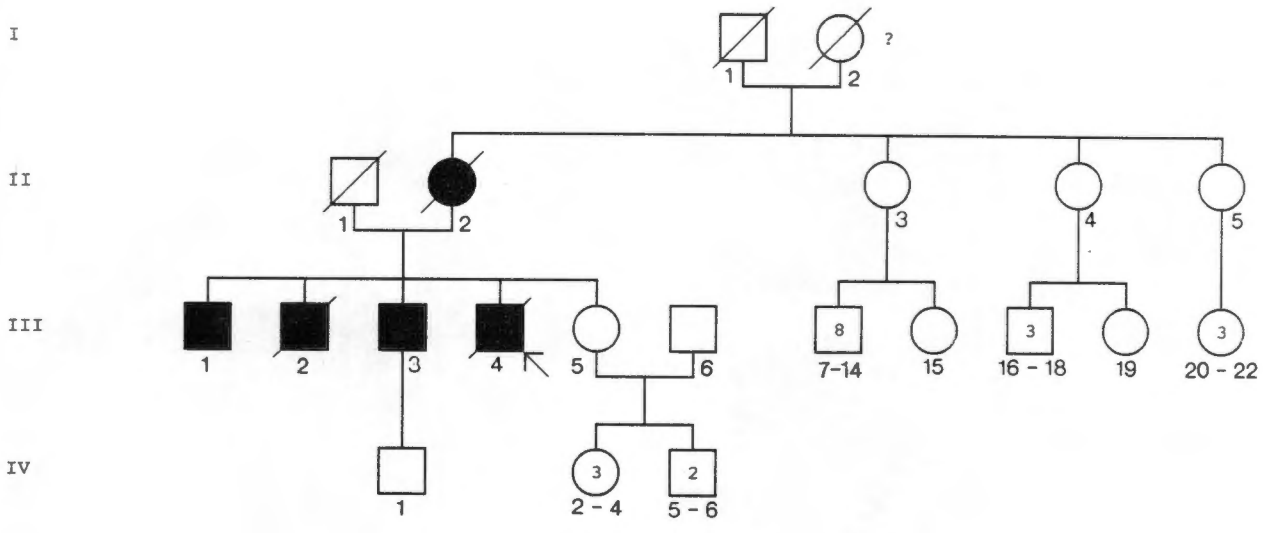

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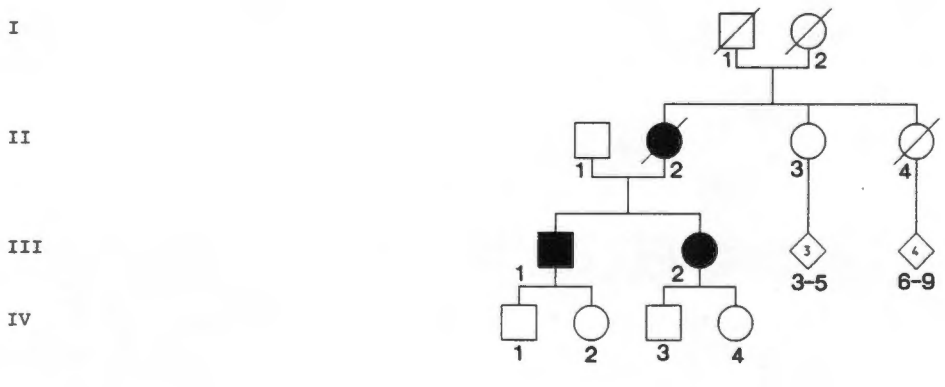

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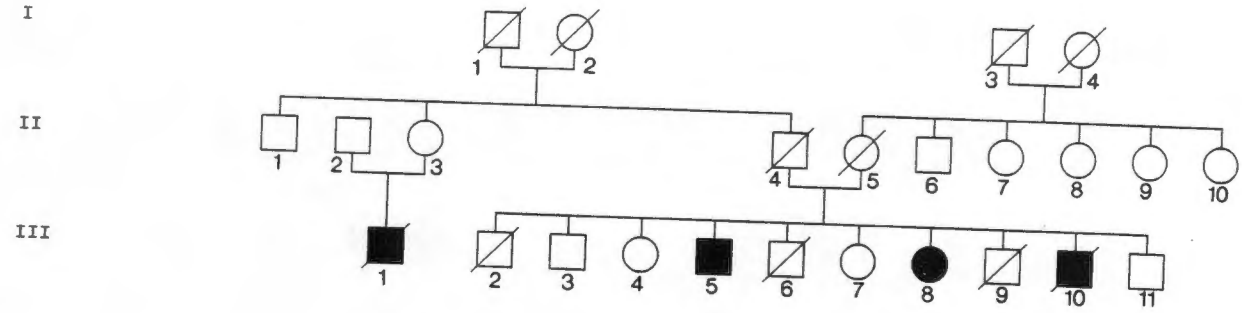

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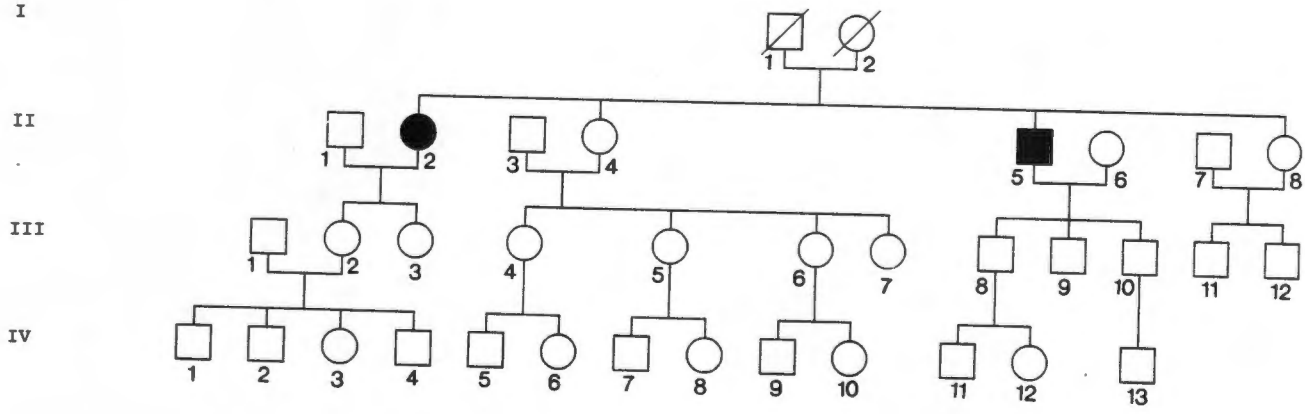

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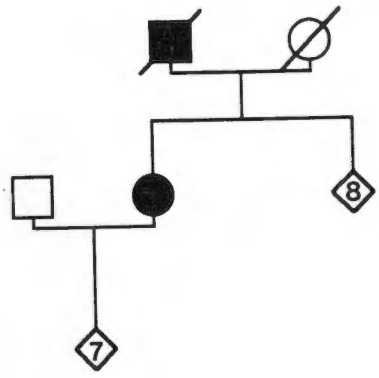

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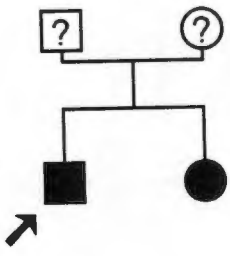

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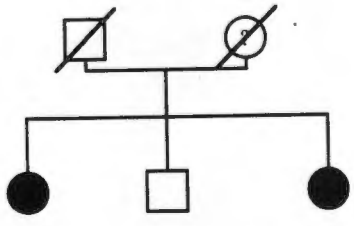

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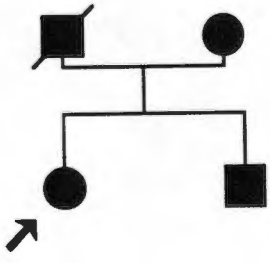

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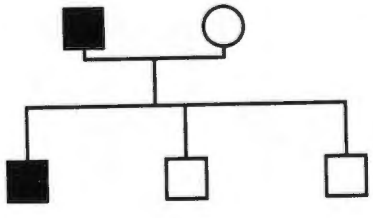

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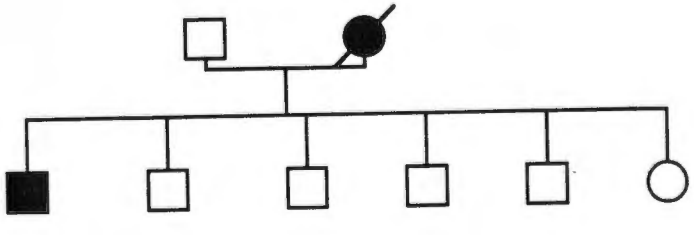


Family X

CLINICAL RECORD

page 1

SURNAME
First name
maiden name
Hospital no.
DOB
race/sex

age of onset

age at 1st assessment
date 1st assessment

age last assessment
date last assessment

SYMPTOMS
prog gait disturbance
freq falls
impaired hand coordn
abn involl movements
speech disturbance
dysphagia
weakness in arms
weakness in legs
visual impairment
hearing loss
impaired mental fuctn
deformity
cardiac symptoms
diabetes
impotence
sphincter disturbance
muscle wasting
muscle cramps
alcohol intake
other symptoms

CLINICAL SIGNS
general
pes cavus
scoliosis
skin
hypogonadism
other

CVS:arrhythmia
cardiac failure
hypertension

optic atrophy
ophthalmoplegia
pigment retinop.
ptosis
horiz nystagmus
vert nystagmus
OKN
eye movements
ocular dysmetria

mental function
cranial nerves
dysarthria
dysphagia

AIMS
fasciculations
muscle wasting
tone RUL
tone LUL
tone RLL
tone LLL
power RUL
power LUL
power RLL
power LLL

tendon reflexes:
bicepsTR R
bicepsTR L
tricepsTR R
tricepsTR L
bracheorTR R
bracheorTR L
kneeTR R
kneeTR L
ankleTR R
ankleTR L
plantar response
clonus
abdom reflexes

sensation:
pain/temp UL
pain/temp LL
vibrn/posn UL
vibrn/posn LL

coordination:
finger-nose
alt/repet
draw designs
heel-shin
toe-finger
truncal sway
stand on 1 leg
intention tremor
GAIT

ATAXIA SCORE

Romberg test
time to reach
dependency:

Scoring system:

Muscle tone score: 1= decreased
2= normal
3= increased
4= markedly increased

tendon reflex score: 1= absent
2= depressed
3= normal
4= increased

sensation score: 1= absent
2= reduced
3= normal

limb coordination score: 1= normal
2= mild
3= moderate
4= severe
5= unable to do

Gait score: 1= normal
2= subjective awareness only
3= definate mild gait ataxia
4= moderate gait ataxia
5= severe, walks with stick
6= chair bound

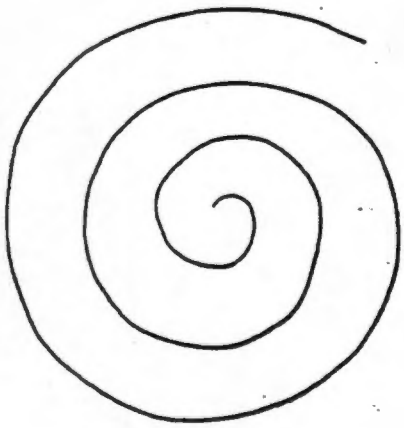
ATAXIA SCORE: 9-10= normal
11-21= mild
22-26= moderate
27-31= moderately severe
>32 = severe

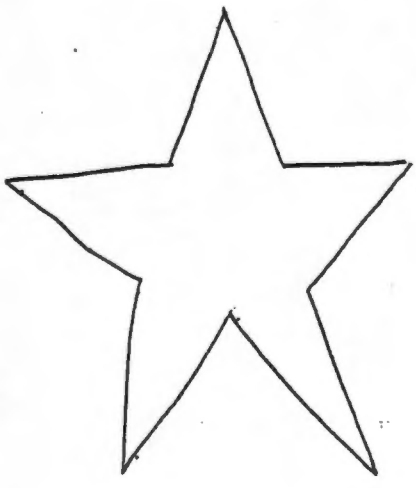
CLINICAL RECORD page 2.

CLINICAL NOTES AND OBSERVATIONS:

SPECIAL INVESTIGATIONS:

COPY DESIGNS:





PUBLICATIONS AND ABSTRACTS RELATING TO THIS THESIS

PUBLICATIONS

Adult onset spinocerebellar ataxia linked to HLA in a South African kindred of mixed ancestry.
A Bryer, R W Martell, ED Du Toit, P Beighton.
Tissue Antigens 1992:40: 111-115

HLA linkage in a kindred with adult-onset spinocerebellar ataxia
RW Martell, A Bryer, P Beighton, E Du Toit.
HLA 1991, volume 2. Editors: Tsuji K, Aizawa M, Sasazuki T.
Oxford:Oxford University Press; 1992:551-554.

Molecular and clinical correlations in spinocerebellar ataxia type 1: evidence for familial effects on the age of onset.
LPW Ranum, M Chung, S Banfi, A Bryer, et al.
American Journal of Human Genetics 1994: IN PRESS.

Hereditary ataxia and related disorders in the Western Cape - a clinical and genetic study.
A Bryer.
Transactions of the College of Medicine of South Africa January-June 1992:40-41.

ABSTRACTS

Spinocerebellar ataxia in South Africa.
A Bryer, RW Martell, P Beighton.
Presented by the author at the 117th annual meeting of the American Neurological Association, October 1992.

Familial spinocerebellar ataxia in Southern Africa.
A Bryer, R Ramesar, P Beighton.
Presented by the author at XVth World Congress of Neurology, September 1993.

HLA linkage in a kindred with adult onset spinocerebellar ataxia.
A Bryer, RW Martell.
Presented by the author at the Annual Congress of the Neurology Association of South Africa, September 1989.

Genetic heterogeneity in familial spinocerebellar ataxia.
A Bryer, RW Martell, P Beighton.
Presented by the author at the Annual Congress of the Neurology Association of South Africa, March 1992.

Spinocerebellar ataxia in South Africa - then and now.
A Bryer, R Ramesar, P Beighton.
Presented by the author at the Annual Congress of the Neurology Association of South Africa, March 1993.

Psychosocial survey in families with familial ataxia.
A Bryer, JC De Villiers, K Weskamp.
Presented by the author at the Annual Congress of the Neurology Association of South Africa, March 1994.

Reprints of the publications listed on the previous page are not included in the appendix in accordance with the regulations of the Doctoral Degrees Board, University of Cape Town.